USE OF LOW-DOSE BETA-BLOCKERS TO TREAT SYMPTOMS OF CHRONIC FATIGUE SYNDROME

by

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STATEMENT OF THESIS APPROVAL

The following faculty members served as the supervisory committee chair and members for the thesis of Christopher Del Allen.

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ABSTRACT

This research explores a possible benefit to chronic fatigue syndrome and myalgic encephalomyelitis (ME/CFS) sufferers with the use of low-dose beta blockers as previous studies show potential for these treatments to lessen the symptoms of pain and fatigue in ME/CFS. Clinical data were collected from 55 patients treated with beta-adrenergic receptor-blocking agents, primarily propranolol, at the Fatigue Consultation Clinic run by Dr. Lucinda Bateman. Patient data were collected before and during treatment with the beta-blocking agents, and statistical analysis identified correlations between treatment and changes in reported measures of fatigue, body aches, pain, headaches, inactivity/function, hours spent vertical in a 24 hour period, and hours spent horizontal in a 24 hour period. After performing statistical analysis on the data, no correlations between the treatment and symptom severity were apparent. However, the subjective nature of the clinical data and the potential for confounding variables warrant a more complete clinical trial.

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CHAPTER 1

LITERATURE REVIEW

Myalgic encephalomyelitis (ME) or chronic fatigue syndrome (CFS) is a complex and debilitating neurological disease affecting multiple biological systems including the immune, endocrine, cardiovascular, and central nervous systems, and aspects of energy metabolism. This constellation of multisystem complications synergistically wreaks havoc on the life of affected individuals. Most patients are no longer able to work, carry on social activities, perform daily activities such as feeding themselves or, in some cases, even get out of bed. ME/CFS can strike anyone at any time, without regard to socioeconomic status or ethnicity.[1] ME/CFS also seems to increase a person's risk of suicide as well as certain types of cancer.[2,3] An estimated one to five million Americans suffer from the condition and the globally estimated prevalence is 0.4-1%.[1,4] Although being female makes a person six times more likely to get ME/CFS, both men and women, old and young, are afflicted.[1,4] Children and adolescents are affected at a similar rate as adults, but have higher rates of recovery than their older counterparts.[1,4] This condition is poorly understood, but millions are desperate for researchers and the medical community to solve the ME/CFS puzzle so sufferers can regain their quality of life.

What causes ME/CFS is still unknown, but research continues as funding allows. A separate theory of the etiology of ME/CFS likely exists for every different researcher.

The medical field is rife with confusion and debate over the various aspects of the illness. One side of the spectrum hypothesizes a biological cause, while the other end postulates a purely psychological etiology of ME/CFS. The truth probably lies somewhere in the middle, but currently, people are left trying to overcome the differences of opinion that abound surrounding the root cause of ME/CFS.

Diagnosis of ME/CFS is perhaps as challenging as identifying a cause. Multiple tests or criteria have been recommended, but a clear cut pathognomonic tool for diagnosis is still lacking. As difficult as accurately diagnosing ME/CFS is, finding a way to treat or possibly cure sufferers far surpasses that challenge. Countless treatment options have been explored both anecdotally and in controlled clinical trials, but very few have shown any reproducible efficacy. Many patients explore mainstream medical treatment options only to turn away with disappointment and seek out alternative options when the former fails them. The relationship between provider and patient is often tenuous as disagreements arise over what the root cause is or what the best approach to treatment may be. Despite all these issues regarding ME/CFS, one thing can be agreed upon: this condition is devastating to all aspects of a person's life.

1.1 History

ME/CFS remains unexplained to date, but research continues to add understanding to its pathogenesis. In 1869 the first publication referencing a condition thought to be ME/CFS identified a disease state called neurasthenia or nervous exhaustion with symptoms including fatigue, headache, impotence, neuralgia, anxiety, and depression.[5] Then in 1904 Angelo Mosso published a landmark manuscript researching the nature of

fatigue that has, to this day, influenced the way fatigue is understood and studied.[6] The evolution of neurasthenia and fatigue continued when in 1938, during the polio epidemic, Alexander Gilliam identified what he called atypical poliomyelitis with symptoms of muscle weakness, clonic twitches and cramps, vasomotor instability, ataxia, severe pain aggravated by exercise, neck and back stiffness, menstrual disturbance and dominant sensory involvement.[7] In 1955 the term myalgic encephalomyelitis (ME) was coined for the condition after an outbreak at a hospital in London[8]. Although these historical cases may not have been what is classified as ME/CFS today, the unique description of the symptomatology in many of the cases strikes an unquestionable resemblance to the current definition of ME/CFS. The name ME remains in use today in much of the world and is often interchangeable with the term CFS. In 1978 the Royal Society of Medicine published a paper describing the symptoms of ME as objective and biological in nature.[9] Since then, the definition and description of the condition has been refined, but researchers remain undecided as to the true nature of ME/CFS.[10] Currently the World Health Organization (WHO) classifies ME as a neurological disease under the International Statistical Classification of Diseases and Related Health Problems 10th Revision.[11] However, the United States Centers for Disease Control and Prevention (CDC) has not adopted the name ME, but instead uses the name CFS. The CDC definition, as seen in Figure 1, focuses more on subjective and somatoform symptoms and puts emphasis on a diagnosis of exclusion of other conditions while the WHO definition focuses more on biological symptoms and has specific criteria that must be met for diagnosis.

The CDC case definition of ME/CFS

- Had six or more months of consecutive fatigue that is not relieved by sufficient bed rest and is not caused by another underlying medical condition.
- The fatigue significantly interferes with daily activities and work.
- The individual concurrently has four or more of the following eight symptoms:
    - Postexertion malaise lasting more than 24 hours
    - Unrefreshing sleep
    - Significant impairment of short-term memory or concentration
    - Muscle pain
    - Multijoint pain without swelling or redness
    - Headaches of a new type, pattern, or severity
    - Tender cervical or axillary lymph nodes.
    - A sore throat that is frequent or recurring.

Figure 1. Diagnostic criteria and ME/CFS case definition of the CDC.

Data Source: (http://www.cdc.gov/cfs/case-definition/1994.html, last accessed October 7, 2014)

These differences in definition lead to confusion and ambiguity for researchers, patients, and the media. Only recently in peer reviewed literature have the two terms been combined as ME/CFS, even though the two names describe the same disease state. The first major U.S. journal article published using the sole title myalgic encephalomyelitis to reference the condition was as recent as 2011 in the Journal of Internal Medicine.[12] Before that, only the titles CFS or CFS/ME appeared in major U.S. publications. Even though the WHO classifies ME/CFS as a disease of the nervous system, many healthcare professionals view it as a psychologically based somatic syndrome with no organic origin. This conflict of opinion has divided the ME/CFS researchers into different camps that tend to focus their research toward their own bias and further obscure the ME/CFS picture.[13] As research advances, the current understanding of ME/CFS will become clearer and help for these individuals will increase.

1.2 Clinical Presentation

In almost every case, ME/CFS begins with a specific stressor, often a viral infection, but can be anything from an auto accident to the death of a loved one.[4] The onset is usually acute and most patients can cite almost to the day when their illness began.[12,14] The initial complaints frequently include fever, lymphadenopathy, abdominal pain, and digestive discomfort as well as nervousness and anxiety about the symptoms, especially as the medical professionals fail to provide an explanation for the symptoms. After a short period of time, fatigue and myalgia become the prominent complaints with particular emphasis on the unique nature of the fatigue that usually appears roughly a day after any physical or mental exertion and lasts for days or weeks.[13] Many people who

have experienced ME/CFS find difficulty in describing the nature of the pain and fatigue associated with the condition, but others have described it as postexertional malaise that occurs 24 to 48 hours after physical or mental activity. Sufferers often say this understates the symptoms. The fatigue debilitates and often leaves the patient unable to walk, stand, or even sit upright following activity, similar to having a dead battery. Some of the more common symptoms documented are impaired mental function and short-term memory difficulties, unrefreshing sleep, migratory arthralgia, unusual headaches, sore throat, chills or sweating, chest pain, visual disturbances, food, drug, or chemical sensitivities, light and temperature sensitivities, orthostatic intolerance (OI), dizziness, loss of balance and coordination, depression, anxiety, moodiness, and menstrual changes in women.[9-20] All these symptoms become exacerbated with physical or mental exertion. The frequency and severity to which these symptoms occur differs widely from one individual to another, but the unique fatigue and postexertional malaise is found in every case of ME/CFS and only found in ME/CFS sufferers.[12] This chronic and persistent combination of symptoms paints a dismal picture for the sufferer. Complete disability is common. Many patients lack the mental capacity or social support to attain help and consequently become isolated, bed bound, and hopeless, with poor quality of life. Many patient support organizations actively search for an explanation to the cause, or at least a laboratory test that could accurately diagnose the condition, to dispel much of the confusion and controversy that surround it, but for now ME/CFS remains a diagnosis of exclusion, and the research pools are muddied with patients who may not actually fit the true diagnostic criteria.

1.3 Diagnosis

Currently, a diagnosis that cannot be made with a positive laboratory test or well defined clinical signs and symptoms must be made by exclusion of all other possibilities. In the United States the most commonly used diagnostic criteria comes from the CDC and was originally proposed by Fukuda and his colleagues.[14] Under these criteria, a diagnosis of ME/CFS is made if a patient meets the criteria listed in Figure 1.

These criteria capture most cases of ME/CFS, but critics say that by following the CDC criteria, many people who do not have ME/CFS may be falsely diagnosed. The inclusion of confounding conditions makes progress in ME/CFS research difficult. Everything from sleep disorders to HIV-AIDS to depression have been placed under the ME/CFS umbrella.[22,23]

In 2011 a group of researchers put together a new diagnostic criteria called the International Consensus Criteria (ICC) (See Appendix A), but it has yet to be adopted widely by the international communities and the United States.[12] The ICC, if adopted, would help remove many of the confounding conditions from research studies because it follows narrow and specific diagnostic guidelines, including compulsory postexertional neuroimmune exhaustion, neurological impairments, immune, gastro-intestinal and genitourinary impairments, and energy production or transportation impairments symptoms. Although not officially used in the USA, many researchers base their research on the more stringent ICC criteria and find stronger correlations in the results of their studies.[24]

Much of the research on ME/CFS has historically focused on one or more specific symptoms, but identifying a root cause remains the ultimate goal of many researchers.

Some of the more promising and investigated theories are a single infectious agent, a hormonal imbalance, neurological abnormalities, immune system dysfunction, mitochondrial dysfunction, genetic predisposition or abnormalities, or a complex combination of these etiologies.

The theory that a single infectious agent causes ME/CFS is most popular in the media and likely the most investigated potential cause. This is for good reason too, as many of the early onset symptoms of the condition resemble other infectious processes. A recurring, relapsing pattern of fever, tender lymph nodes, gastrointestinal distress, fatigue, and myalgia are commonly found in many viral or bacterial infections. From early in the history of the illness, infectious agents were considered. One theory suggested that the polio virus caused CFS/ME, but no virus was found, thus the name atypical polio was given.[7] Another theory suggests that ME/CFS is a chronic form of Lyme's disease caused by *Borrelia burgdorferi*.[25] Epstein-Barr virus has been implicated and shown some clinical evidence of an association with ME/CFS, but the nature of that association has not been identified.[26] Human herpes viruses 6 and 7 have also been explored with no causal link.[27,28] Human retroviruses including human T-cell lymphotropic virus II (HTLV-II), JHK virus (JHKV), and xenotropic murine leukemia virus-related virus (XMRV) have brought the ME/CFS community to the edge of its collective seat, but no identifiable link has been found between the viruses and the condition.[29,30] Coxsackievirus, cytomegalovirus, mycoplasma, and various fungal theories have arisen, been researched and then been pushed aside over the years.[4,31] Indeed, it seems the investigative world targets a new pathogen every few years, but repeatedly, the research ends with no more than a handful of questions and some weak

links between the organism in question and ME/CFS. It may be that the root cause of the condition begins with a change in the nervous or immune system that leads to increased risk of infectious processes, or perhaps multiple pathogens are capable of triggering a common pathway.

ME/CFS appears even more complex when investigating the hormonal imbalances of the condition. The hypothalamo-pituitary-adrenal (HPA) axis has been blamed for many of the symptoms of ME/CFS, and it may yet prove to be an important factor, but once again, the HPA axis does not seem to be the root cause of the condition, but merely a secondary complication. Patients show dysregulation of different hormones at various times throughout the illness.[32,33] At the onset of being sick, a person usually has some kind of physical, emotional, or mental stressor that triggers an increase in cortisol and cortisol releasing hormone (CRH) levels. This hormone increase upregulates the immune system and other body systems in healthy controls and ME/CFS sufferers alike, but studies demonstrate a significant decrease in cortisol and CRH levels of ME/CFS patients when compared to control groups. This depressed cortisol response seen in ME/CFS sufferers still falls within the clinically normal range and is therefore not detected by many clinicians. Despite significant differences in these patients, cortisol cannot be used as an ME/CFS biomarker. Other studies show that cortisol replacement does not significantly benefit the ME/CFS patient. Other hormonal imbalances are also common in ME/CFS patients. Growth hormone, leptin, and melatonin have been implicated and found to have subtle abnormalities in the patient population; however, like all other avenues explored to date, these are not significant or reproducible enough as a diagnostic tool or even to explain the symptoms of the condition.[34]

Investigators of the neurological symptoms found in ME/CFS have identified abnormalities with functional magnetic resonance imaging (fMRI) and single-photon emission computed tomography (SPECT) scanning, but cannot show that these tests are specific or sensitive enough for diagnosis.[35,36] Research continues into the neurological basis of the condition and as greater understanding into how the integrity and functionality of the neurological system impacts the body, a clearer understanding of the symptoms unique to ME/CFS may emerge. Current research is looking for potential neurological biomarkers for ME/CFS such as neuropeptide Y (NPY). NPY is a stress mediator found in the central and peripheral nervous system. Plasma levels of the stress induced peptide increase in times of systemic illnesses such as systemic lupus erythematosus and rheumatoid arthritis. A study looking for potential ME/CFS biomarkers demonstrated that NPY is significantly elevated in ME/CFS sufferers compared to controls showing an altered stress response in this population.[37] The study correlates with others by implicating the HPA axis as a major component of ME/CFS

The published literature also shows that the immune system is a major player in ME/CFS. Natural killer (NK) cells and cytokines have reduced function in patients with ME/CFS. Specifically, NK cells have deficiencies in perforin and granzymes and appear to be reduced in number.[38] Cytokine profiles seem abnormal in ME/CFS patients with a tendency toward the proinflammatory response as well as an elevated number of lymphocytes expressing dipeptidyl peptidase IV (DPPIV). The measurement of NK activity along with DPPIV expression on the lymphocytes are predictable markers in identifying patients with ME/CFS, but more work is necessary to show reproducibility and specificity for ME/CFS.[39]

Another advancement in developing a functional diagnostic tool for ME/CFS is mitochondrial function testing. A group of researchers have shown that ATP production and mitochondrial function in ME/CFS patients is significantly reduced compared with the control group. They have also shown that the severity of the patient's condition correlates to the dysfunction of the mitochondrial function and energy production.[40] The researchers are not clear on whether the mitochondrial dysfunctions are the primary cause of the condition or just a secondary effect of an upstream problem, but mitochondrial dysfunction relates to many symptoms suffered by ME/CFS patients as well as people suffering with other chronic conditions with similar symptoms.[40]

While research continues on chemical and microbiological methods of diagnosis, more promising methodologies using molecular methods and advanced genetic modeling studies to identify individuals who may be genetically predisposed with increased risk of ME/CFS and other diseases may be more fruitful. A recent study found nine genes using microarray and quantitative polymerase chain reaction (qPCR) methods that are strongly associated with ME/CFS. The genes identified, STAT5A, PSMA4, PSMA3, HINT1, DBI, COX5B, ATP5J2, GZMA, and RHOC, associate with various aspects of the immune system, cellular transport, or receptor/binder interactions.[41] This study was limited in scope, but further studies are underway to identify more correlations between these genes and symptoms of ME/CFS. Another study found seven genomic subtypes of ME/CFS and related the genotypes to different phenotypes. The genetic profiles formed using clustering of qPCR data revealed these clinical subtypes: subtype 1 (cognitive, musculoskeletal, sleep, anxiety/depression); subtype 2 (musculoskeletal, pain, anxiety/depression); subtype 3 (mild); subtype 4 (cognitive); subtype 5 (musculoskeletal,

gastrointestinal); subtype 6 (postexertional); subtype 7 (pain, infectious, musculoskeletal, sleep, neurological, gastrointestinal, neurocognitive, anxiety/depression).[42] These subtypes may prove useful in further isolating patient populations for research and treatment purposes. A third study, published by researchers at the University of Utah, investigated the gene expression of ME/CFS patients after exertion. This study found significant results offering a possible explanation for the postexertional fatigue and malaise experienced in ME/CFS. Thirteen genes were studied using mRNA extracted and measured by qPCR. The study identified four classes of severity in the patient population with matching control groups. The gene expression of each of the genes, ASIC3, P2RX4, P2RX5, TRPV1, ADRA2A, ADRB1, ADRB2, COMT, IL6, IL10, LTA, TLR4, and CD14 is shown in Figure 2.[43] The study demonstrated a positive correlation between the severity of the symptoms a patient experiences and the increased expression of the selected genes. Isolating only a few of these genes, P2RX4, LTA, ADRB2, and IL10, as biomarkers after moderate exercise yielded a sensitivity of 0.93 and a specificity of 0.77 with an accuracy of 0.80.[43] These indicators show that these tests are potentially effective diagnostic biomarkers for ME/CFS, but work remains to show reproducibility and to further isolate subtypes based on gene expression patterns. Another finding in the gene expression studies is that the genes under investigation typically are not expressed during times of viral infection, but may lead to increased risk of acquiring a viral infection. This may explain the confounding influence pathogens have had since the start of the ME/CFS investigation, and why none of these theories have panned out as the root cause of ME/CFS.[44]

Further genetic research focuses on the HPA axis to find biomarkers because many

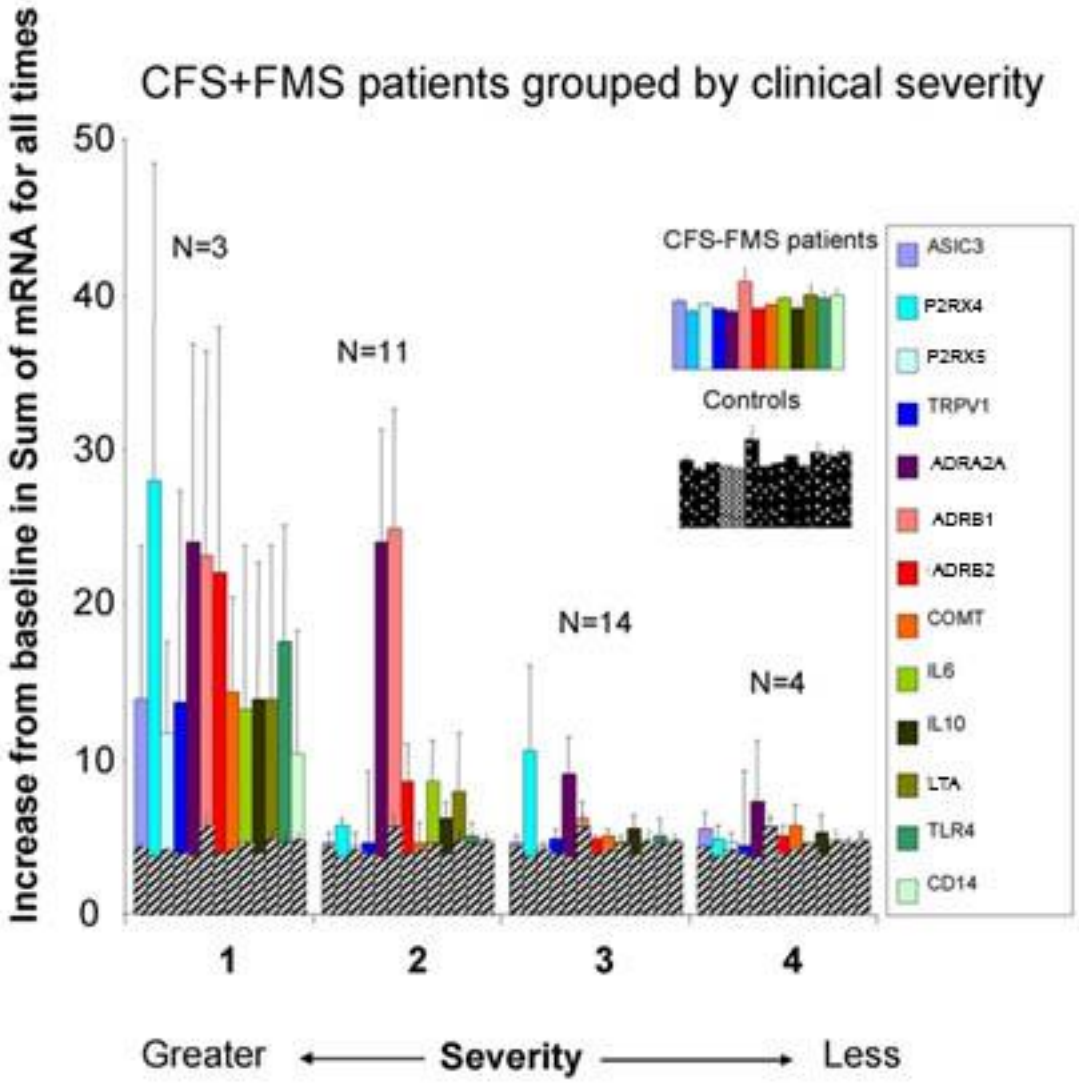


Figure 2. Histogram of genetic expression of sixteen genes associated with ME/CFS grouped in four classes of symptom severity in ME/CFS patients.

(Data Source: Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC: Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. J Intern Med 2012, 271:64-81)

studies show significant deviation from the normal population in ME/CFS patients.[32] Researchers at the CDC identified single nucleotide polymorphisms in the glucocorticoid receptor gene (NR3C1) as having a strong correlation with ME/CFS patients. These studies showed that the NR3C1 gene was affected by gene-environment interactions and attempted to explain part of the etiology of ME/CFS as regulated by environmentally influenced changes in NR3C1 gene expression.[45] The changes in this gene, along with other receptor genes, are enlightening the ME/CFS pathophysiology and may explain the HPA involvement in the condition, but that is only part of the clinical picture.

1.4 Treatment

The prognosis for ME/CFS is bleak at best. Although the condition does not significantly increase mortality, the quality of life for the sufferers is so poor that suicide is one of the three leading causes of death, following heart disease and cancer.[22] Due to the unclear etiology and no known and testable biomarkers for ME/CFS, current treatments tend to focus on alleviating symptoms rather that addressing the root cause of the illness. Two major schools of thought exist regarding treatment; those who believe ME/CFS is psychologically based and those who believe ME/CFS is biologically based.

Psychologically based researchers gravitate towards treatments such as cognitive behavioral therapy (CBT) that attempts to reshape the way a patient views themselves and the illness that they are living with. CBT improves the quality of life of ME/CFS sufferers according to peer reviewed studies.[46] However, this does not prove or disprove the psychosomatic hypotheses as other organically based conditions, such as multiple sclerosis and ovarian cancer, are also helped by CBT.[47,48] CBT can help people learn to

deal with the daily challenge posed by any chronic condition, including ME/CFS, and play an important role in alleviating suffering and helping these people regain some functionality.

Pacing of daily activities and stress reduction are another psychologically based way to cope with the chronic condition of ME/CFS and shows reduction in symptoms in many patients. The concept involves changing one's life to match the energy capacity of one's body and practicing biofeedback and stress reducing activities such as yoga, breathing exercises and meditation. If patients learn to reduce stress and avoid exceeding their energy expenditure threshold, they can avoid symptom flares. These techniques can improve the quality of life of the ME/CFS sufferer, but oftentimes drastic reductions in work, family, and social activities must be made to stay below a person's energy expenditure threshold and remove the stresses of daily living.[49]

Another treatment strategy that shows some validity in clinical trials is graded exercise therapy (GET). GET protocol asks the patient to gradually increase volume and intensity of exercises they do over an extended period of time trying not to exceed their energy limit and trigger a symptom flare. A patient may start out by walking from the bed to the couch one day and the next day they may do that same activity twice. Eventually, some patients demonstrate marked improvement in their exercise capacity and can even return to most activities of daily living. However, most patients do not make significant gains with GET, and it rarely significantly alleviates a patient's symptoms over time.[50]

Along with activity modifying treatment strategies, pharmaceutical treatments also abound. Many patients are in chronic pain, develop depression or anxiety secondary to their ME/CFS, and have difficulty sleeping. As a result, many different pharmaceuticals

target these symptoms with some success. Selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, sleep aids, anxiolytics, and other pain medications help alleviate these specific symptoms or comorbidities of ME/CFS. Other alternative treatment protocols such as naturopathic or dietary supplementation have not proven universally acceptable for the treatment of ME/CFS, although many patients use them and claim to benefit from them.[49,51]

One promising pharmaceutical treatment option is the use of low-dose beta blockers to help patients have more energy, less pain, and potentially spend more time upright and active. Beta-adrenergic antagonists function through nonselective binding to the beta receptors primarily found on smooth muscle tissues of the heart, airways, arteries, kidneys and other tissues of the sympathetic nervous system. The blockade inhibits the binding of the catecholamines epinephrine and norepinephrine, blocking the effects of these stress hormones that include increased heart rate, blood pressure, blood glucose levels, and the general upregulation of the sympathetic nervous system. This general function of inhibiting the stress response leads to a number of medical uses for beta blockers including treatment of essential tremor, migraine, hypertropic subaortic stenosis, mitral valve prolapse, myocardial infarction, pheochromocytoma, atrial fibrillation, congestive heart failure, performance anxiety, and postural orthostatic tachycardia syndrome (POTS).[52-56] Propranolol is administered orally and is lipophilic with high absorbance rates. (Data Source: http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid =c5091cd2-81c8-4ffe-b2aa-d053de5d6e12, last accessed October 8, 2014) The typical propranolol dose for the aforementioned conditions ranges from 80mg to up to 240mg daily. Previous studies show that doses closer to 40mg daily may be effective at

alleviating pain in some chronic pain conditions.[55] Additionally, higher doses may lead to premature fatigue, which is one of the cardinal symptoms of ME/CFS.[57]

Although none of these treatments cure ME/CFS, some individuals have shown long-term remission using a combination of approaches. Part of the challenge of treating a condition such as this is that there is no clear cause to target. It is very likely that as research continues, several different causes will emerge that all lead to the same manifestation of symptoms. Only then will a treatment strategy truly target the root cause, or causes, of ME/CFS.

CHAPTER 2

METHODS

2.1 Introduction to Methods

The aim of this study is to test the hypothesis that low-dose beta blockers are effective at improving symptoms of ME/CFS sufferers. This theory has been tested by other studies that show how low-dose propranolol can help reduce fatigue and pain.[57] The present study builds on previous work by gathering historical clinical data from the Fatigue Consultation Clinic run by Dr. Lucinda Bateman. The patients were selected that have been treated with low-dose beta blockers to examine the effects, whether positive or negative, on their symptoms and identify any correlations between the treatment and symptom improvement. This pilot-study approach to research is an effective way to take a snapshot of the situation without expending exorbitant resources, but is limited in its ability to control for variables that exist in historical clinical data.

2.2 Subjects

Patients of Dr. Lucinda Bateman at the Fatigue Consultation Clinic in Salt Lake City, Utah were selected for inclusion in this study based on a review of medical records. Dr. Bateman has been using low-dose beta blockade for treatment of POTS and OI symptoms as well as pain and fatigue associated with ME/CFS for several years and has an

accessible database of patient records for this study. The electronic files at the clinic were retrospectively term-searched for propranolol and metoprolol. Any individual who had used these medications or had been counseled to try them as a treatment modality were included in the preliminary data analysis. Additionally, Dr. Bateman assisted in manual identification of patients not found in the electronic records search who were treated with beta blockers. Each patient selected met the ICC diagnostic criteria for CFS. The date range for the data collected began on 3/23/05 and ended on 5/13/13. A total of 55 patient matches met the search criteria and were included in the study.

2.3 Data

The Fatigue Consultation Clinic uses an intake questionnaire (see Appendix B) that assesses patient symptoms on each visit. These self-evaluations were used to score each patient in categories of fatigue, body aches, pain, headaches, inactivity/function, hours spent vertical in a 24 hour period, and hours spent horizontal in a 24 hour period for each patient on each visit date. The scale for each question ranged from one to ten with one being the least severe symptoms and ten being the most severe. The questionnaire was changed in March of 2011 with the removal of the question for inactivity/function and the addition of the question for number of hours spent vertical and number of hours spent horizontal. These two questions were not scaled on a one to ten scale but were recorded in hours spent in each activity. The data prior to the change was converted to the 24 hour scale by using 17 hours as the maximum time a person would spend vertical and converting the one to ten scores to a 24 hour scale. The variables were then combined to create one variable from the inactivity/function variable and the hours spent vertical

variable. Two questions were listed for pain: body aches and pain. These scores were combined and averaged into one pain score for each visit date in an effort to measure overall pain. The individual pain questions of body aches and pain were also left separated in the analysis. Demographic data, dates of visits, and medication information were also collected from the questionnaires for each visit. Data from all clinic visit dates during beta blocker treatment were collected as well as up to three visit dates prior to the beginning of treatment, when available. The data were compiled in a spreadsheet and analyzed in RStudio for correlations between beta blocker treatment and symptom severity. Subjective comments related to propranolol or metoprolol treatment from patients in their medical records were also recorded and clarified by Dr. Bateman when needed.

2.4 Analysis

A total of 156 visits were recorded for the 55 patients and all visits were included in the analysis. Using R and RStudio, the data were compiled and analyzed for statistical correlations. Graphical representation with boxplots of the data were created using the ggplot package to visualize any relationships within each variable between the before and after measures (see Appendix C). Following this step, scatterplots were made between each variable to identify any relationships between the variables and changes caused before or after beta blocker treatment (see Appendix D). Following graphical exploration of the relationships between all variables in the dataset, statistical analysis was performed using the parametric Welch two sample t-test and the nonparametric Kruskal-Wallis test. All relationships were nonsignificant at the $\alpha=.05$ level with the most significant

relationship demonstrating a p value of 0.0685 for the correlation between headaches and beta blocker treatment (See Appendix E). A multiple linear regression model using a n response variable created by combining the hours spent vertical variable with the variable inactivity/function converted to a 24 hour scale showed no significant relationships in the data between any of the variables, but showed once again that headaches and pain were the most strongly influenced variables from the beta blockade with p values of 0.0982 and 0.1020, respectively (See Appendix F). Further analysis was not warranted by the nonsignificant findings of this preliminary investigation. The demographic data for the study are summarized in Appendix G.

CHAPTER 3

DISCUSSION

3.1 Significance of Findings

Although no statistically significant findings presented themselves, some observations are worth discussion and further investigation. Twenty-five of the 55 patients (46%) included in the study noted some improvement of symptoms when on propranolol or metoprolol. Fourteen of the 55 patients (25%) reported negative effects ranging from increased fatigue to suicidal ideations. Sixteen of the 55 patients (29%) did not report any effect either positive or negative. These data are presented visually in Figure 3. Although more patients appear to benefit from treatment, these data must be interpreted in the context of being recorded by the prescribing physician and the patients who want the treatment to work and are looking for any benefit and possibly downplaying any negative effects. Table 1 lists clinical notes on patient responses to propranolol or metoprolol treatment. The table shows tremor and POTS are frequently alleviated by beta blockade, whereas common side effects include gastrointestinal symptoms, increased fatigue, and tiredness. Some patients respond well while others display only negative effects. Some patients benefited, but also displayed side effects to the medications. These patients were classified as positive or negative responders based on the overall benefit observed by the clinician. The demonstration of side effects in

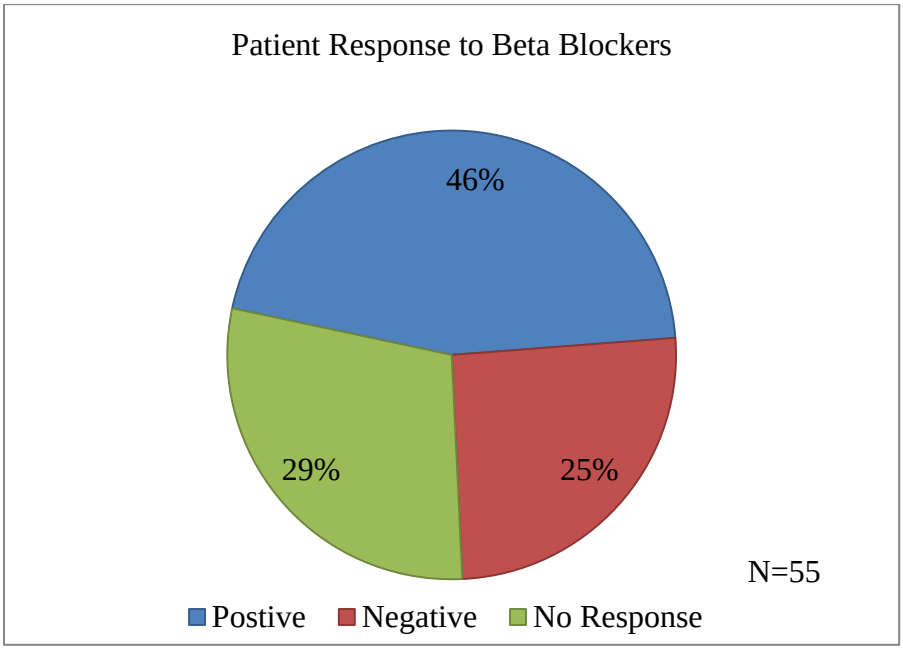


Figure 3. The relative percentages of patient responses to treatment with beta blockers based on clinical notes.

Table 1

Patient's subjective reporting of the effects of treatment with beta blockers.

Positively responding patients	Negatively responding patients
1. feels less dizzy, heart rate increase less dramatic on challenge, 2. saw improvement in trembling and severe illness, 3. helps with tremor and anxiety, 4. fewer lows, 5. has added benefit, helped her to be up longer, improved function, 6. more active, more energy, generally doing well, 7. tremor and handwriting a bit improved, 8. mild improvement attributed to propranolol, does notice a difference when taken, 9. less dizzy, fewer headaches, helps POTS, 10. effective for tremor, feels better, essential tremor much better, helps with OI and pain, 11. headaches and resting pulse better, tolerates more activity, 12. not making her tired, POTS seems better 13. helpful for treating autonomic overload symptoms, 14. better control of tachycardia, 15. helpful to control OI, 16. POTS and tachycardia better, 17. helps with performance anxiety, better control of blood pressure, 18. feeling better overall with more energy, 19. improves tachycardia, 20. pulse and blood pressure swings are less dramatic, 21. less malaise and anxiety, 22. more active, less depressed, 23. helps POTS, 24. increased activity, 25. POTS better,	1. caused fatigue, hot flashes and aches, 2. caused bradycardia, dizziness and OI, 3. caused bradycardia, causes headaches, nausea, and hypertonia arterialis, 4. contributes to fatigue, caused nausea and vomiting, 5. caused nocturnal diarrhea, 6. increased sleepiness and fatigue, 7. caused brain fog, 8. multiple side effects, interfering with other medications, 9. increased tiredness, too tired and depressed, 10. allergic to propranolol, 11. worsening depression with suicidal ideation, 12. felt flat, tired, sleepy, 13. autonomic symptoms worse, 14. bradycardia, brain fog,

some patients while others displayed only positive responses gives more credence to the findings of other researchers that have shown possible genetic subtypes of ME/CFS that respond to beta-blockade treatment more favorably than others.[41,43]

Figure 4 shows a comparison of gene expression in ME/CFS patients, one male and one female treated with propranolol as well as four age and gender matched controls. These data suggest that with more research, potential genetic subtypes of patients with ME/CFS could be identified that would respond favorably to specific treatments as well as those who should not be treated with them. Postulation aside, the current data show that nearly half of the patients selected for this study reported some beneficial effect of using low dose beta-blockers. This is a promising and exciting observation and although many limitations exist in the current study, further work should be performed to more thoroughly explore the effects of beta blockade on ME/CFS patients.

3.2 Limitations and Future Work

The study design investigating the effects of low dose beta-blockers on ME/CFS limited the potential outcome. The study population was selected retrospectively and variables with potential influence on the outcome were not controlled for. Some of these confounding variables may include subclassifying patients by gender or age, interfering medications or treatment modalities and dosing, reporting biases or misattribution of symptoms and side effects, and lack of uniform and clearly defined definitions of symptom reporting by patients. No subgroups were formed and no division of the data was made by age or gender. This division, if used in future studies, may help identify a population that responds better to the treatment. Some patients were recently diagnosed

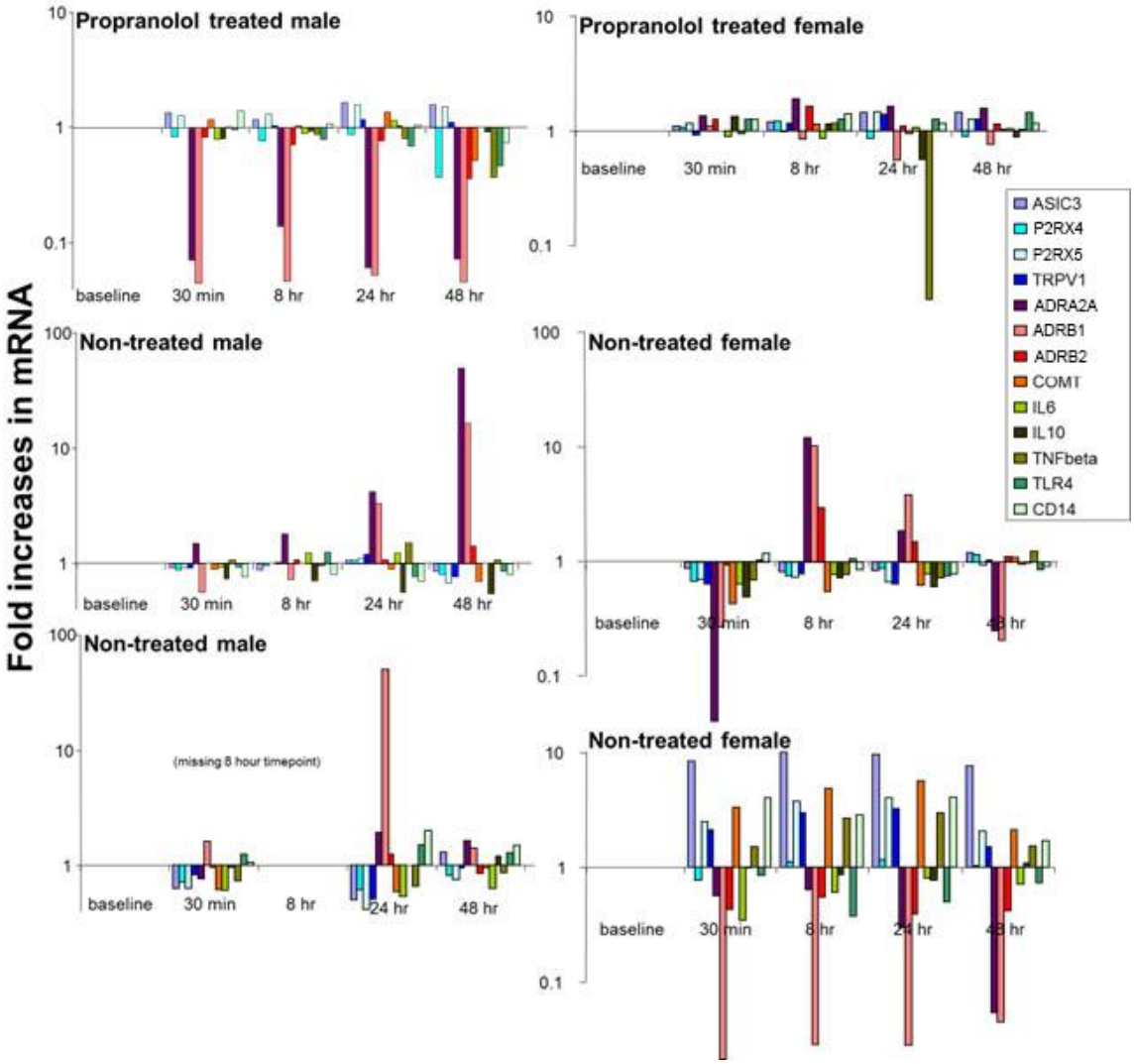


Figure 4. A comparison of the activation of 13 genes in matched untreated and propranolol treated individuals after an exercise challenge.

(Unpublished data provided by Alan R. Light)

while others have been struggling with symptoms for decades. Some patients had up to 12 different medications that could have contributed to the outcome in any number of unknown ways. Further control for variables such as these could have masked statistically significant results. With a carefully designed clinical trial for propranolol or other beta-blocker treatment of ME/CFS, significant results may be observed and patient care improved with its use. There may also be a subgroup of ME/CFS sufferers that have specific genetic profiles that can be isolated. Some genotypes may be more responsive to beta-blockade than other genotypes. Isolation of these genotypes could not only yield better treatment results, but may allow research protocols that have failed to find significance in the past to find useful results in the search for the ME/CFS root cause. Further studies should be designed with more control over variables and subclassifying patient populations.

3.3 Conclusions

ME/CFS is a serious condition that cripples the lives of people young and old every day. Even a slight improvement in functionality for these individuals could give them more productive and meaningful lives and benefit society. Research into methods to treat and improve the symptoms of this population should continue at a more rapid pace. There is much potential for improvement of our understanding of the pathophysiology of this disease and how to more effectively treat it. With more research, low dose beta-blockers may yet prove to be efficacious in reducing the symptom load of ME/CFS sufferers, but this treatment method will not be a cure. If a root cause or perhaps multiple causes are discovered, a way to prevent or possibly even cure this disabling disease may present

itself. Until that time, treatment modalities, such as beta-blockades, may allow ME/CFS patients to have some semblance of normal, functional lives.

APPENDIX A

INTERNATIONAL CONSENSUS

CRITERIA

Table 2

Myalgic encephalomyelitis: international consensus criteria.

Adult and paediatric, clinical and research

Myalgic encephalomyelitis is an acquired neurological disease with complex global dysfunctions. Pathological dysregulation of the nervous, immune and endocrine systems, with impaired cellular energy metabolism and ion transport are prominent features. Although signs and symptoms are dynamically interactive and causally connected, the criteria are grouped by regions of pathophysiology to provide general focus.

A patient will meet the criteria for postexertional neuroimmune exhaustion (A), at least one symptom from three neurological impairment categories (B), at least one symptom from three immune/gastro-intestinal/genitourinary impairment categories (C), and at least one symptom from energy metabolism/transport impairments (D).

A. Postexertional neuroimmune exhaustion (PENE pen'-e): Compulsory

1. Marked, rapid physical and/or cognitive fatigability in response to exertion, which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.

Operational notes: For a diagnosis of ME, symptom severity must result in a significant reduction of a patient's premorbid activity level. Mild (an approximate 50% reduction in pre-illness activity level), moderate (mostly housebound), severe (mostly bedridden) or very severe (totally bedridden and need help with basic functions). There may be marked fluctuation of symptom severity and hierarchy from day to day or hour to hour. Consider activity, context and interactive effects. Recovery time: e.g. Regardless of a patient's recovery time from reading for ½ hour, it will take much longer to recover from grocery shopping for ½ hour and even longer if repeated the next day – if able. Those who rest before an activity or have adjusted their activity level to their limited energy may have shorter recovery periods than those who do not pace their activities adequately. Impact: e.g. An outstanding athlete could have a 50% reduction in his/her pre-illness activity level and is still more active than a sedentary person.

Table 2 continued

Adult and paediatric, clinical and research
B. Neurological impairments At least one symptom from three of the following four symptom categories
1. Neurocognitive impairments
a. Difficulty processing information: slowed thought, impaired concentration e.g. confusion, disorientation, cognitive overload, difficulty with making decisions, slowed speech, acquired or exertional dyslexia
b. Short-term memory loss: e.g. difficulty remembering what one wanted to say, what one was saying, retrieving words, recalling information, poor working memory
2. Pain
a. Headaches: e.g. chronic, generalized headaches often involve aching of the eyes, behind the eyes or back of the head that may be associated with cervical muscle tension; migraine; tension headaches
b. Significant pain can be experienced in muscles, muscle-tendon junctions, joints, abdomen or chest. It is noninflammatory in nature and often migrates. E.g. generalized hyperalgesia, widespread pain (may meet fibromyalgia criteria), myofascial or radiating pain
3. Sleep disturbance
a. Disturbed sleep patterns: e.g. insomnia, prolonged sleep including naps, sleeping most of the day and being awake most of the night, frequent awakenings, awaking much earlier than before illness onset, vivid dreams/nightmares
b. Unrefreshed sleep: e.g. awaken feeling exhausted regardless of duration of sleep, day-time sleepiness

Table 2 continued

Adult and paediatric, clinical and research
b. Motor: e.g. muscle weakness, twitching, poor coordination, feeling unsteady on feet, ataxia
Notes: Neurocognitive impairments, reported or observed, become more pronounced with fatigue.Overload phenomenamay be evident when two tasks are performed simultaneously. Abnormal accommodation responses of the pupils are common. Sleep disturbancesare typically expressed by prolonged sleep, sometimes extreme, in the acute phase and often evolve into marked sleep reversal in the chronic stage. Motor disturbances may not be evident in mild or moderate cases but abnormal tandem gait and positive Romberg test may be observed in severe cases.
C. Immune, gastro-intestinal and genitourinary impairments At least one symptom from three of the following five symptom categories
1. Flu-like symptoms may be recurrent or chronic and typically activate or worsen with exertion. e.g. sore throat, sinusitis, cervical and/or axillary lymph nodes may enlarge or be tender on palpitation
2. Susceptibility to viral infections with prolonged recovery periods
3. Gastro-intestinal tract: e.g. nausea, abdominal pain, bloating, irritable bowel syndrome
4. Genitourinary: e.g. urinary urgency or frequency, nocturia
5. Sensitivities to food, medications, odours or chemicals
Notes: Sore throat, tender lymph nodes, and flu-like symptoms obviously are not specific to ME but their activation in reaction to exertion is abnormal. The throat may feel sore, dry and scratchy. Faucial injection and crimson crescents may be seen in the tonsillar fossae, which are an indication of immune activation.

Table 2 continued

Adult and paediatric, clinical and research
D. Energy production/transportation impairments: At least one symptom
1. Cardiovascular: e.g. inability to tolerate an upright position - orthostatic intolerance, neurally mediated hypotension, postural orthostatic tachycardia syndrome, palpitations with or without cardiac arrhythmias, light-headedness/dizziness
2. Respiratory: e.g. air hunger, laboured breathing, fatigue of chest wall muscles
3. Loss of thermostatic stability: e.g. subnormal body temperature, marked diurnal fluctuations; sweating episodes, recurrent feelings of feverishness with or without low grade fever, cold extremities
4. Intolerance of extremes of temperature
Notes: Orthostatic intolerance may be delayed by several minutes. Patients who have orthostatic intolerance may exhibit mottling of extremities, extreme pallor or Raynaud's Phenomenon. In the chronic phase, moons of finger nails may recede.
Paediatric considerations Symptoms may progress more slowly in children than in teenagers or adults. In addition to postexertional neuroimmune exhaustion, the most prominent symptoms tend to be neurological: headaches, cognitive impairments, and sleep disturbances.
1. Headaches: Severe or chronic headaches are often debilitating. Migraine may be accompanied by a rapid drop in temperature, shaking, vomiting, diarrhoea and severe weakness.
2. Neurocognitive impairments: Difficulty focusing eyes and reading are common. Children may become dyslexic, which may only be evident when fatigued. Slow processing of information makes it difficult to follow auditory instructions or take notes.

Table 2 continued

Adult and paediatric, clinical and research
All cognitive impairments worsen with physical or mental exertion. Young people will not be able to maintain a full school programme. 3. Pain may seem erratic and migrate quickly. Joint hypermobility is common. Notes: Fluctuation and severity hierarchy of numerous prominent symptoms tend to vary more rapidly and dramatically than in adults. Classification ——— Myalgic encephalomyelitis ——— Atypical myalgic encephalomyelitis: meets criteria for postexertional neuroimmune exhaustion but has a limit of two less than required of the remaining criterial symptoms. Pain or sleep disturbance may be absent in rare cases. Exclusions: As in all diagnoses, exclusion of alternate explanatory diagnoses is achieved by the patient's history, physical examination, and laboratory/biomarker testing as indicated. It is possible to have more than one disease but it is important that each one is identified and treated. Primary psychiatric disorders, somatoform disorder and substance abuse are excluded. Paediatric:'primary' school phobia. Comorbid entities: Fibromyalgia, myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, Raynaud's phenomenon, prolapsed mitral valve, migraines, allergies, multiple chemical sensitivities, Hashimoto's thyroiditis, Sicca syndrome, reactive depression. Migraine and irritable bowel syndrome may precede ME but then become associated with it. Fibromyalgia overlaps.

APPENDIX B

INTAKE QUESTIONNAIRES

NAME: **DATE:**

List all medications and dosage schedule:

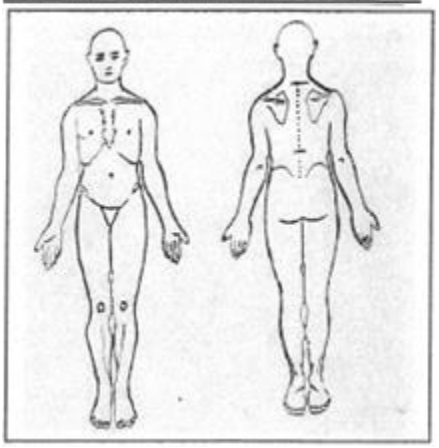
1.	6.	11.
2.	7.	12.
3.	8.	13.
4.	9.	14.
5.	10.	15.

SYMPTOM SCORES

FATIGUE	0	1	2	3	4	5	6	7	8	9	10
DEPRESSION*ANXIETY	0	1	2	3	4	5	6	7	8	9	10
BRAIN FOG	0	1	2	3	4	5	6	7	8	9	10
BODY ACHES	0	1	2	3	4	5	6	7	8	9	10
PAIN	0	1	2	3	4	5	6	7	8	9	10
HEADACHES	0	1	2	3	4	5	6	7	8	9	10
SLEEP PROBLEMS	0	1	2	3	4	5	6	7	8	9	10
INACTIVITY/function	0	1	2	3	4	5	6	7	8	9	10

0= GOOD (least) **10= BAD (most)**

COLOR IN ALL PAIN AREAS IN RED INK



What do you want to discuss or work on today?

1)

2)

3)

PHYSICAL EXAMINATION:

WT:
BP:
P:

- ❍ Mental Status: alert, oriented
- ❍ Eyes/PERRL_____
- ❍ TM's_____
- ❍ Throat_____
- ❍ Carotids R 0 1+ 2+; L 0 1+ 2+. Bruits R L
- ❍ Thyroid _____
- ❍ Nodes_____
- ❍ Lungs_____
- ❍ Axillae_____
- ❍ Heart_____
- ❍ Breast_____
- ❍ Abdomen_____
- ❍ Inguinal nodes pos neg_____
- ❍ Leg edema (R: 0 , tr, 1+ 2+; L: 0, tr, 1+ 2+)
- ❍ Pedal pulses Right DP PT Left DP PT
- ❍ Skin_____

NEURO: ❍ CN II-XII

- ❍ Reflexes (0, 1+, 2+ on body diagram)
  Babinski pos R L neg R L
- ❍ Motor: Walks on heels, toes. Squats.
  Grip_____. Pronator drift_____
- ❍ Sensory: (describe)_____
- ❍ Cerebellar F➔N normal or_____
  Tandem Gait normal or_____
- ❍ Rhomberg-- neg pos

- ❍ Tender Points (● on diagram) _____ /18
- ❍ OTHER_____

Figure 5. Intake questionnaire used prior to March 2011.

NAME: **EMAIL:** **DATE:**

1.	6.	11.
2.	7.	12.
3.	8.	13.
4.	9.	14.
5.	10.	15.

SYMPTOM SCORES BEST (least) WORST (most)

FATIGUE	0	1	2	3	4	5	6	7	8	9	10
DEPRESSION*ANXIETY	0	1	2	3	4	5	6	7	8	9	10
BRAIN FOG	0	1	2	3	4	5	6	7	8	9	10
BODY ACHES	0	1	2	3	4	5	6	7	8	9	10
PAIN	0	1	2	3	4	5	6	7	8	9	10
HEADACHES	0	1	2	3	4	5	6	7	8	9	10
SLEEP PROBLEMS	0	1	2	3	4	5	6	7	8	9	10

Hours vertical/24 hours 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15+
(average time with feet on the floor---sitting, standing or walking)

Hours horizontal/24 hours 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15+
(average time with feet up— resting in recliner, feet up, napping, sleeping in bed)

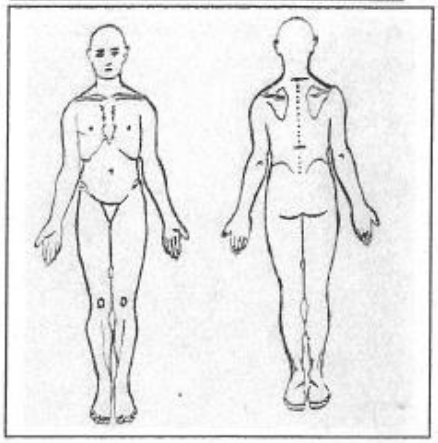
What do you want to discuss or work on today?

1)

2)

3)

COLOR IN ALL PAIN AREAS IN RED INK



PHYSICAL EXAMINATION:

WT:
BP:
P

☐ Mental Status: alert, oriented

☐ Eyes/PERRL_____
☐ TM's_____
☐ Throat_____
☐ Carotids R 0 1+ 2+; L 0 1+ 2+. Bruits R L
☐ Thyroid _____
☐ Nodes_____
☐ Lungs_____
☐ Axillae_____
☐ Heart_____
☐ Breast_____
☐ Abdomen_____
☐ Inguinal nodes pos neg_____
☐ Leg edema (R: 0 , tr, 1+ 2+; L: 0, tr, 1+ 2+)
☐ Pedal pulses Right DP PT Left DP PT
☐ Skin_____
NEURO: ☐ CN II-XII
☐ Reflexes (0, 1+, 2+ on body diagram)
Babinski pos R L neg R L
☐ Motor: Walks on heels, toes. Squats.
Grip_____ Pronator drift_____
☐ Sensory: (describe)_____
☐ Cerebellar F to N normal or_____
Tandem Gait normal or_____
☐ Rhomberg-- neg pos
☐ Tender Points (☐ on diagram) ____ /18
☐ OTHER_____

Figure 6. Intake questionnaire used after March 2011.

APPENDIX C

BOXPLOT COMPARISONS

BETWEEN VARIABLES

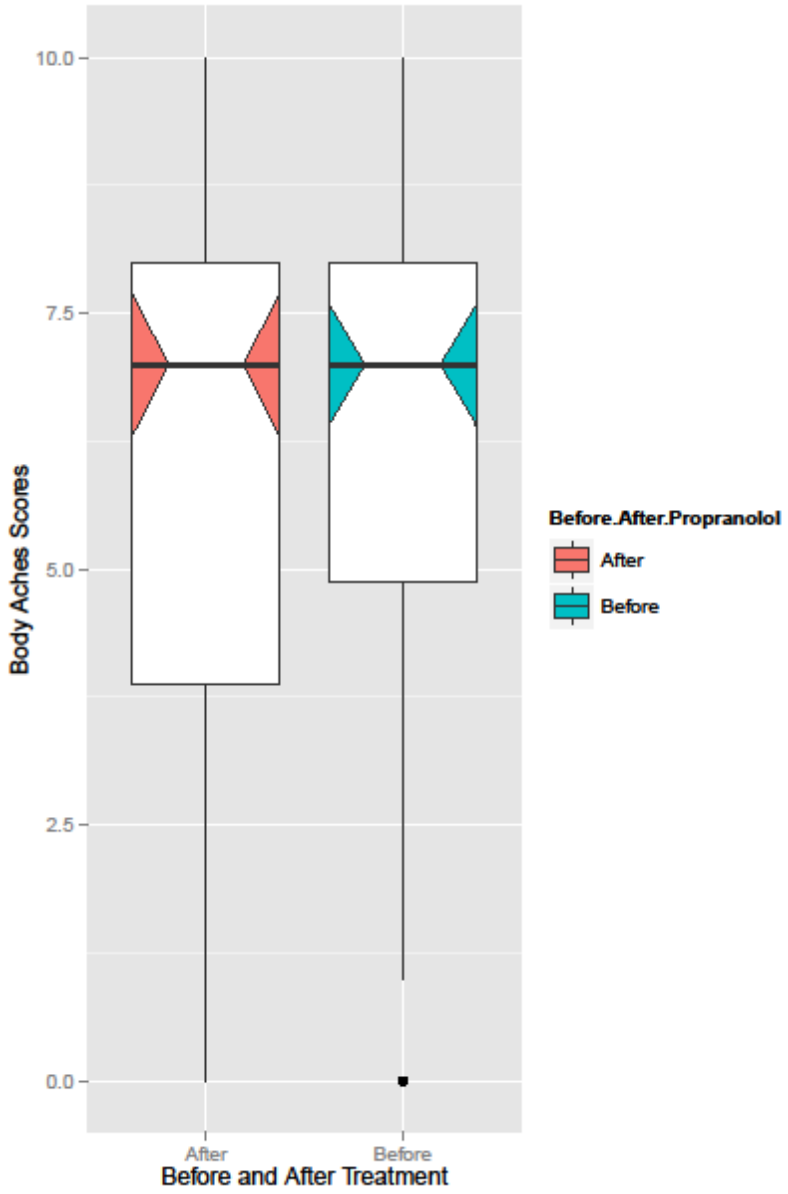


Figure 7. Boxplot comparing body aches scores before and after propranolol treatment.

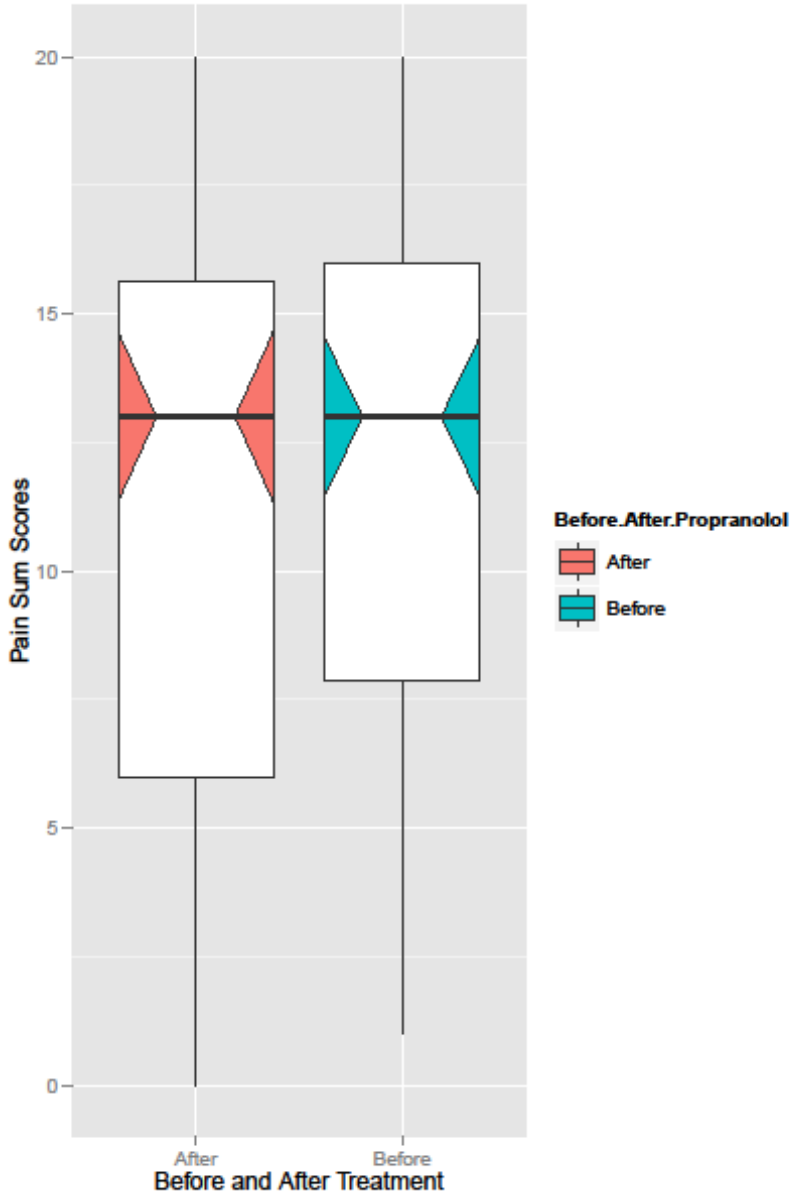


Figure 8. Boxplot comparing pain sum scores before and after propranolol treatment.

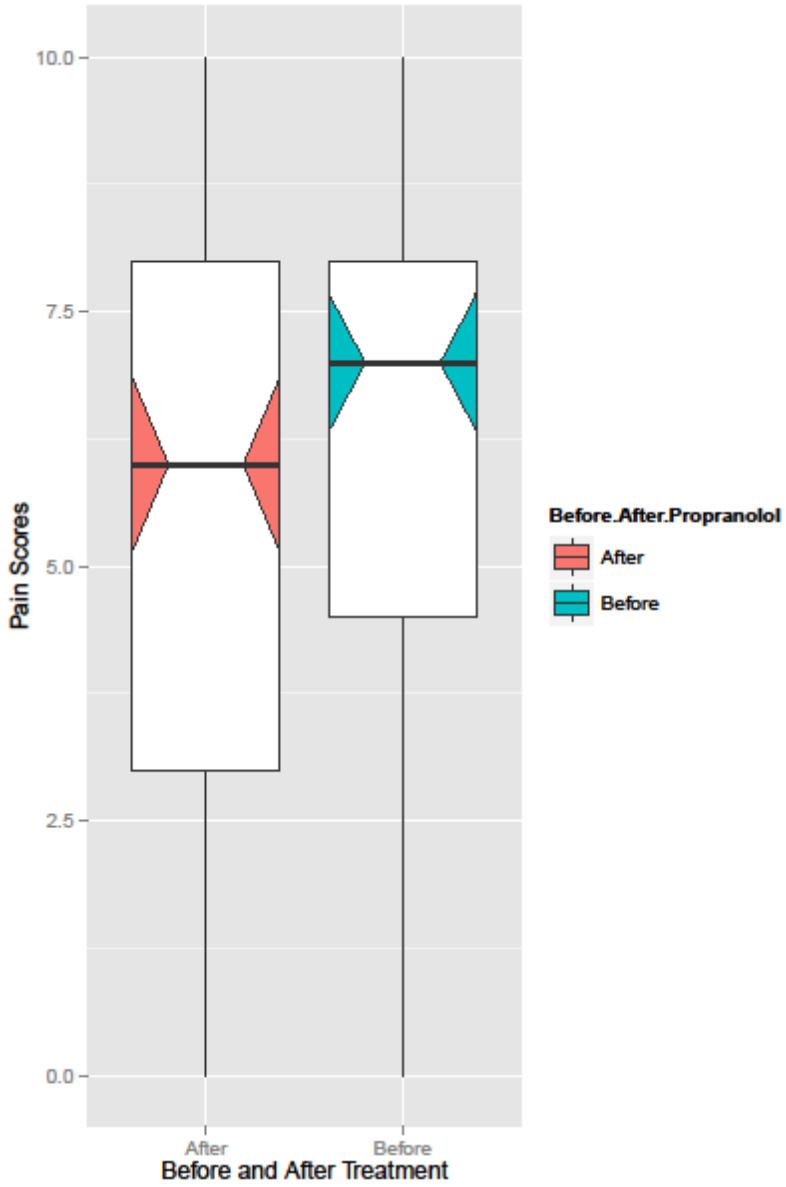


Figure 9. Boxplot comparing pain scores before and after propranolol treatment.

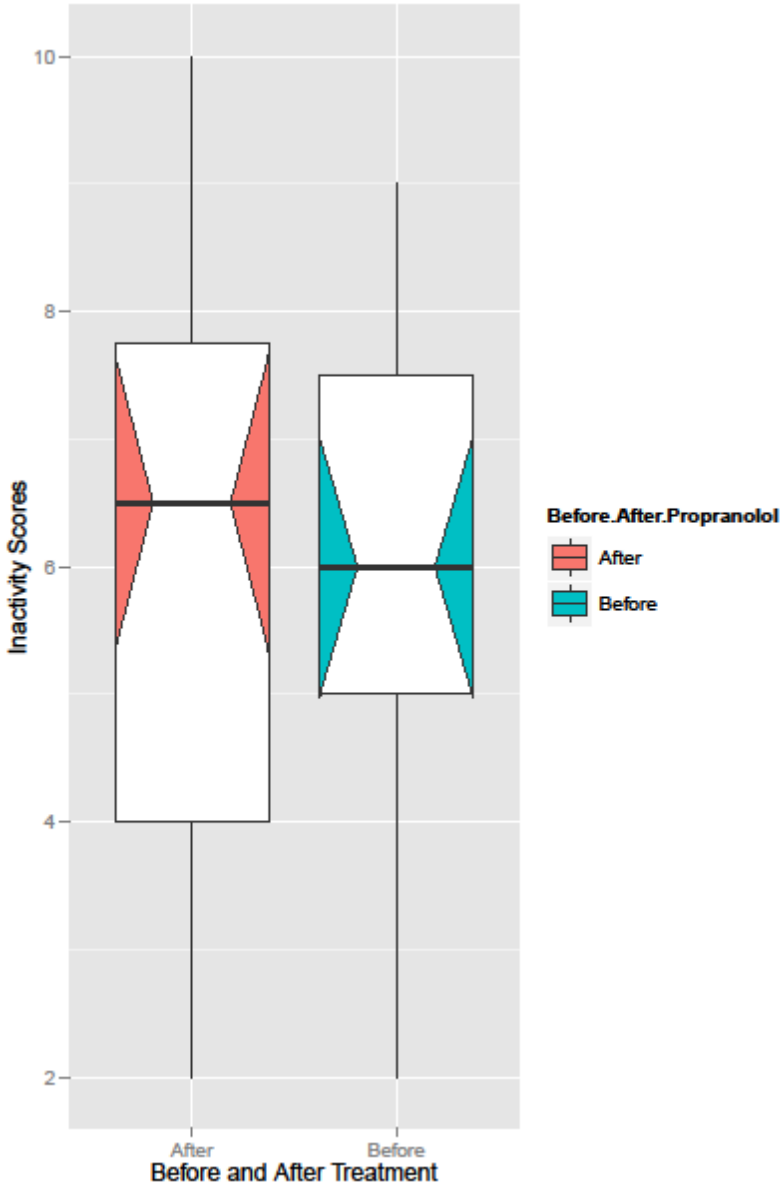


Figure 10. Boxplot comparing inactivity scores before and after propranolol treatment.

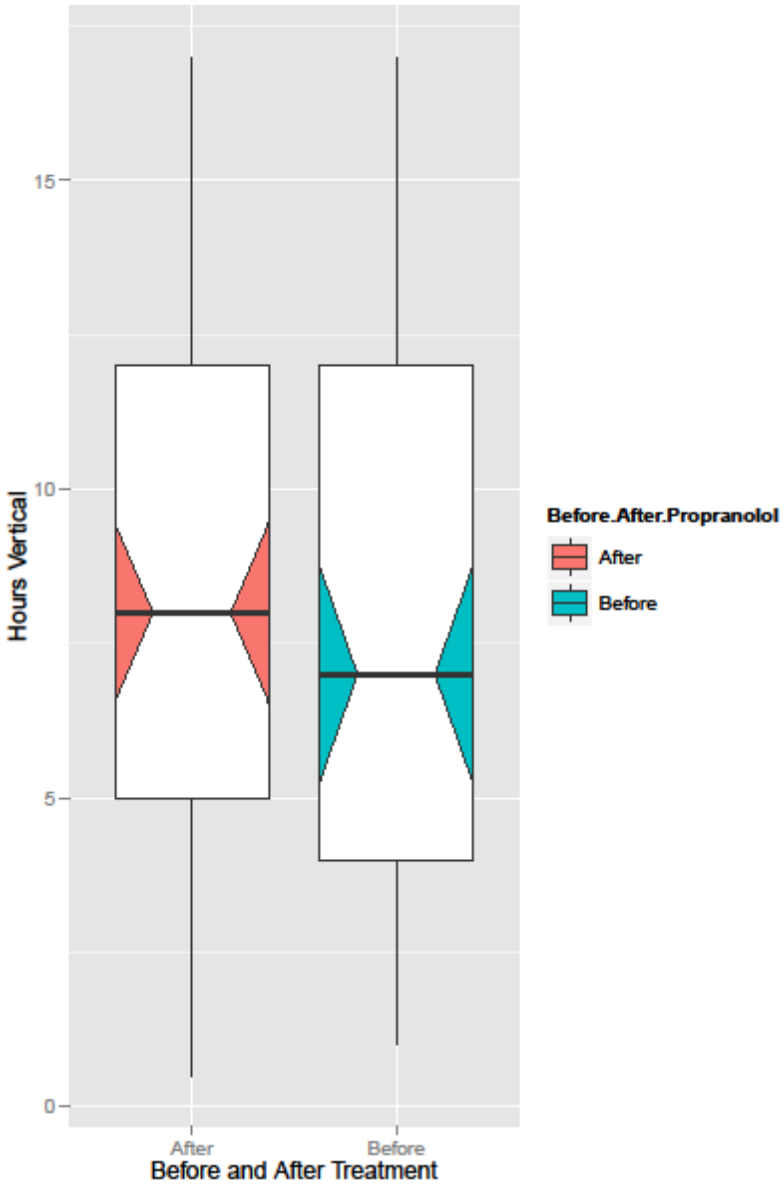


Figure 11. Boxplot comparing hours vertical before and after propranolol treatment.

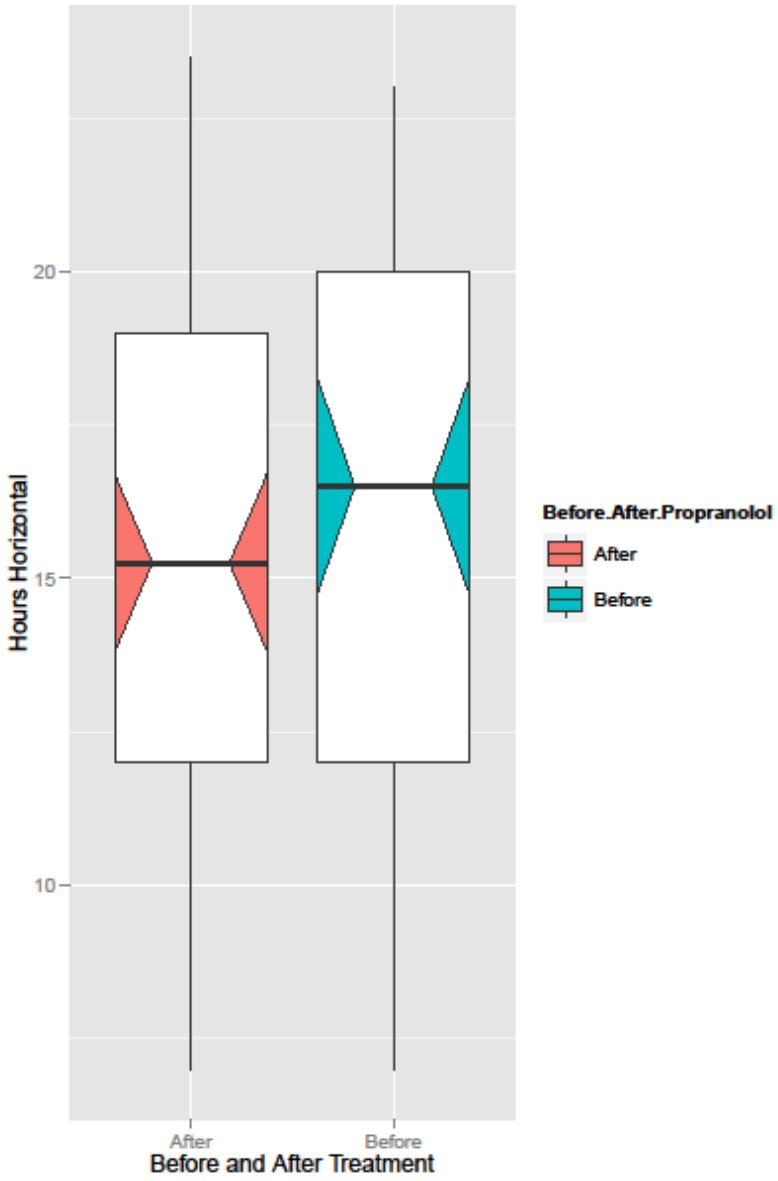


Figure 12. Boxplot comparing hours horizontal before and after propranolol treatment.

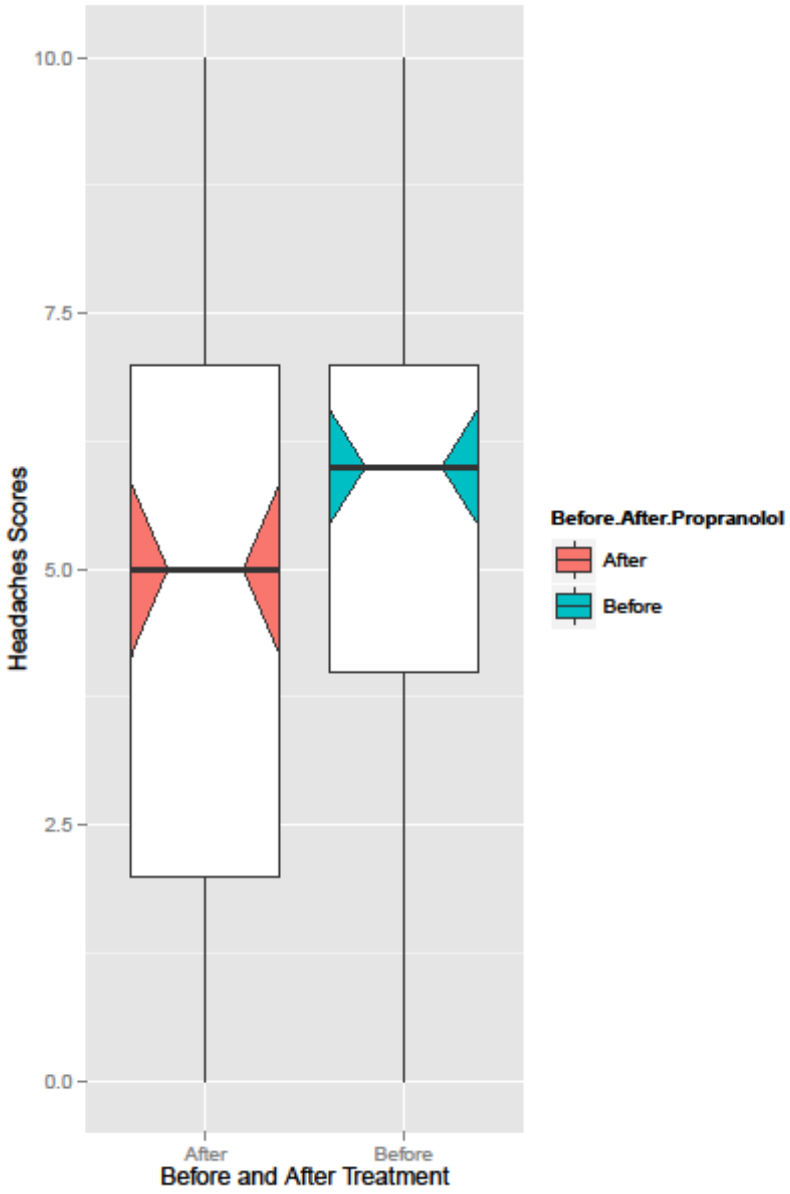


Figure 13. Boxplot comparing headaches scores before and after propranolol treatment.

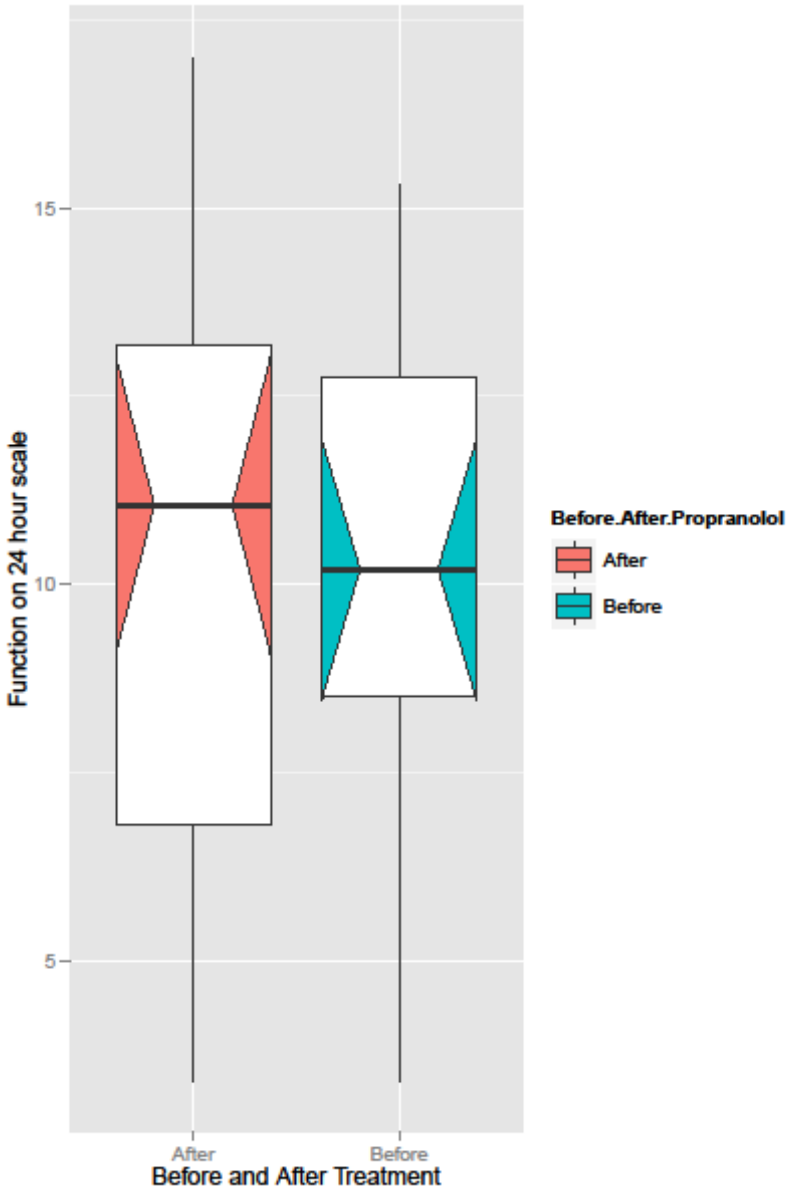


Figure 14. Boxplot comparing function on a 24 hour scale before and after propranolol treatment.

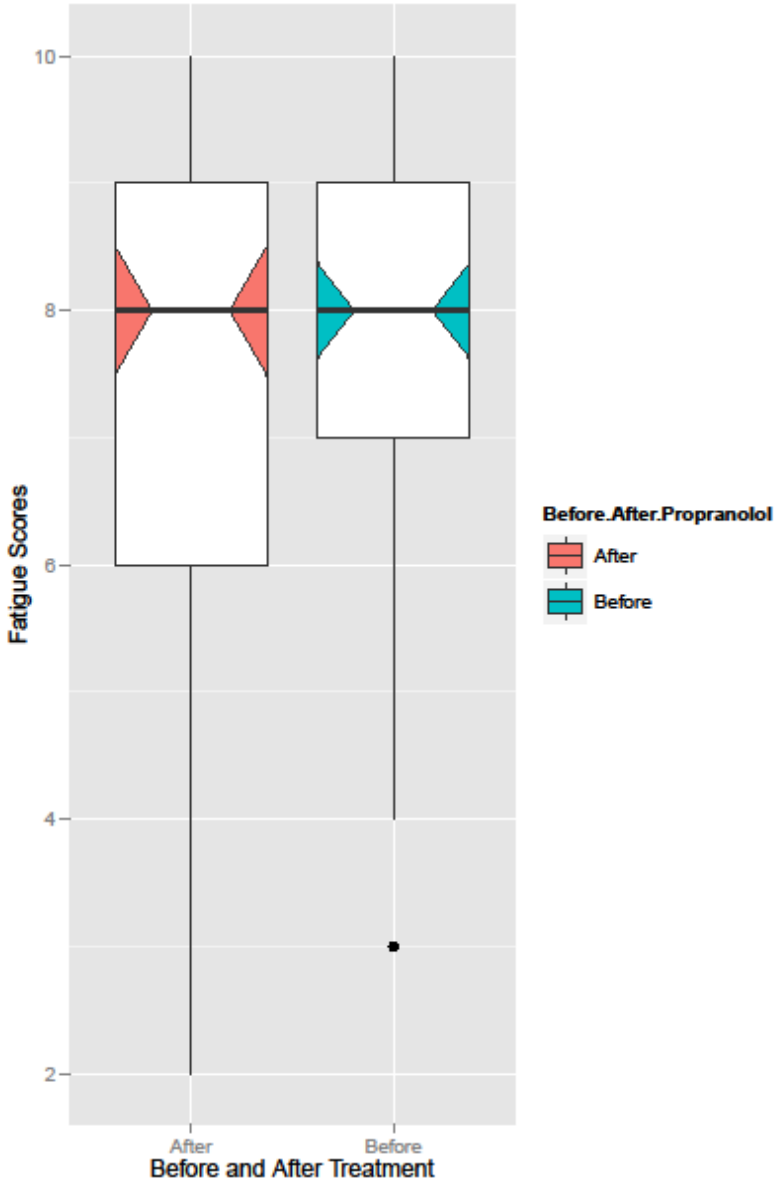


Figure 15. Boxplot comparing fatigue scores before and after propranolol treatment.

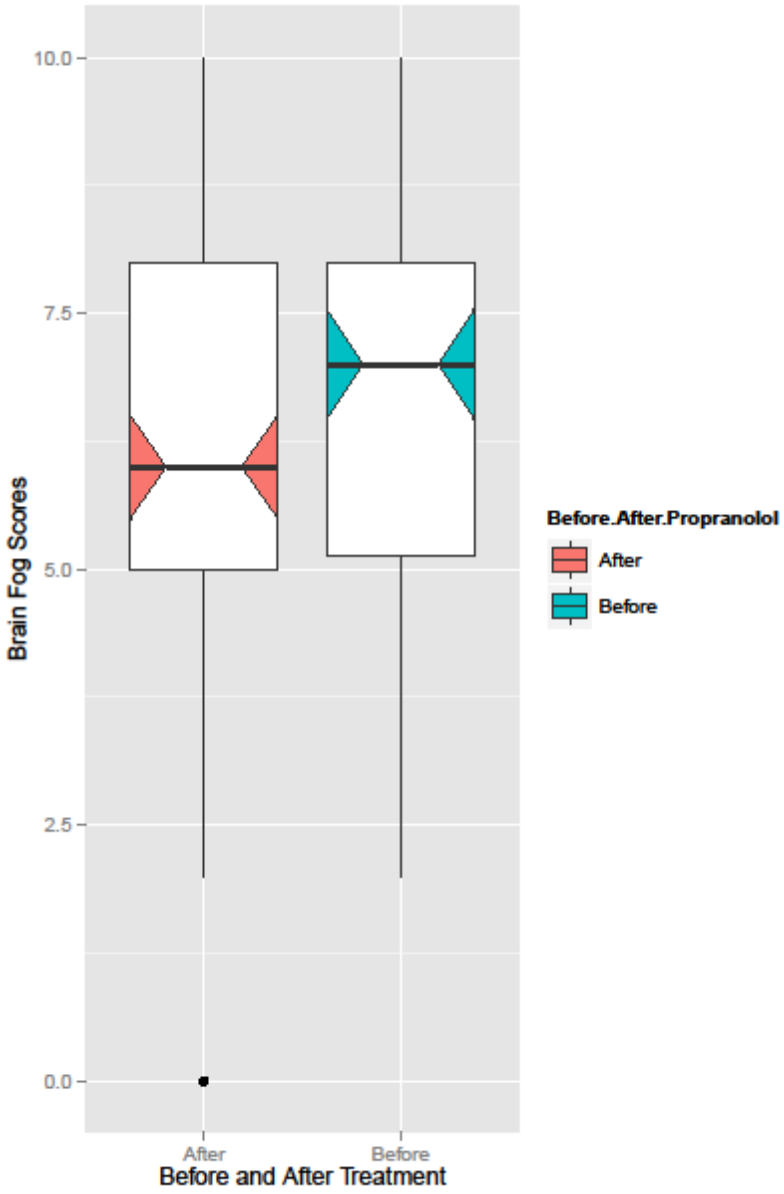


Figure 16. Boxplot comparing brain fog scores before and after propranolol treatment.

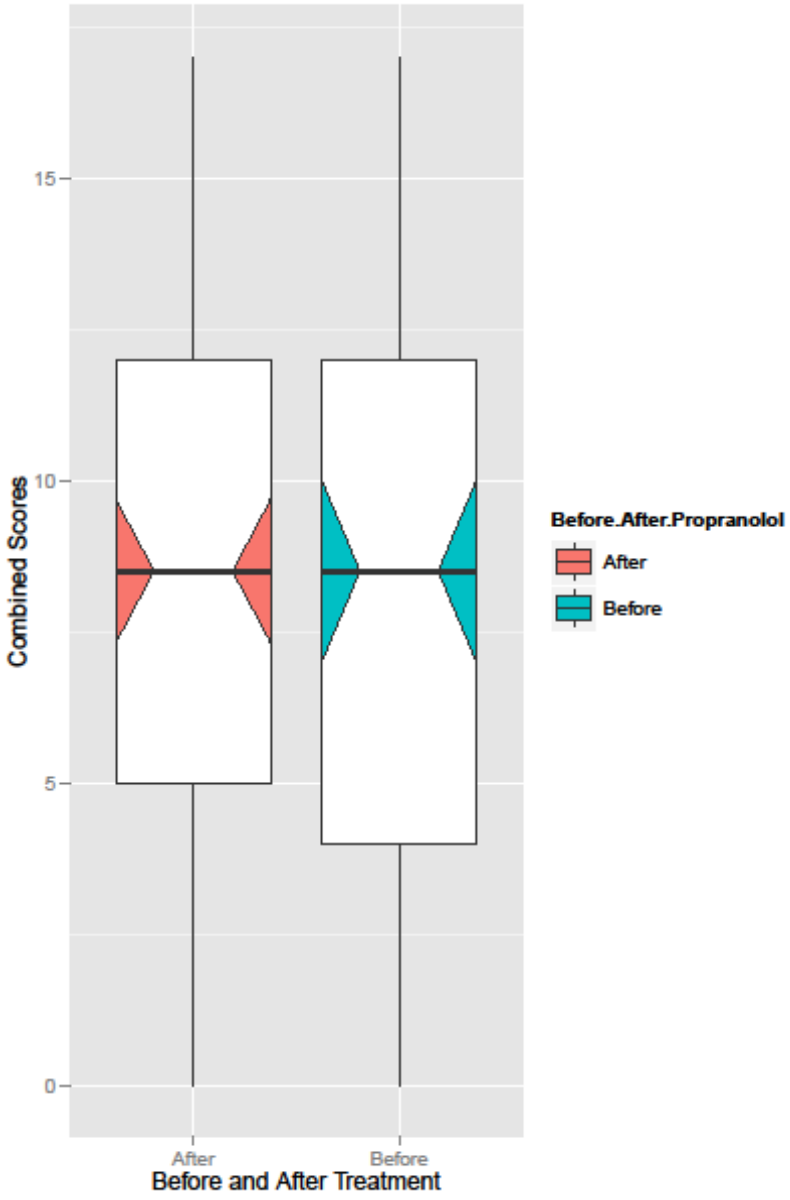


Figure 17. Boxplot comparing combined activity scores before and after propranolol treatment.

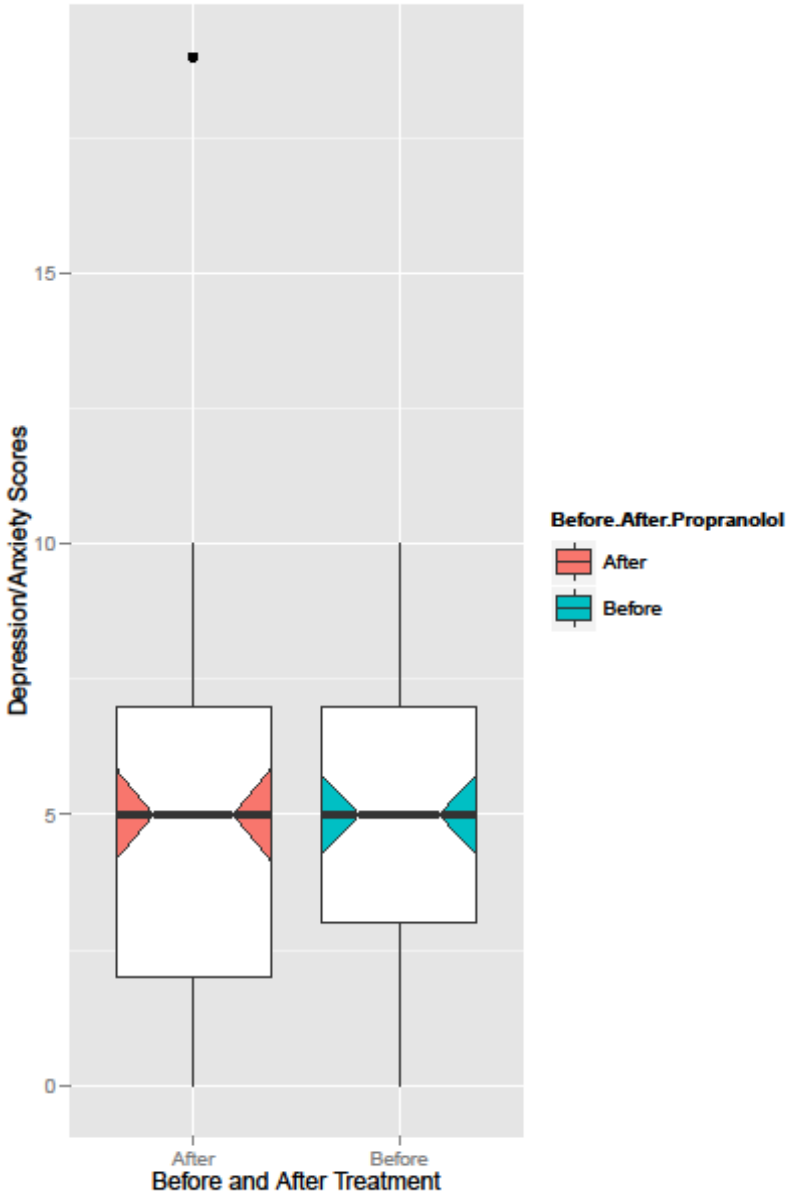


Figure 18. Boxplot comparing depression/anxiety scores before and after propranolol treatment .

APPENDIX D

SCATTERPLOT COMPARISON

BETWEEN VARIABLES

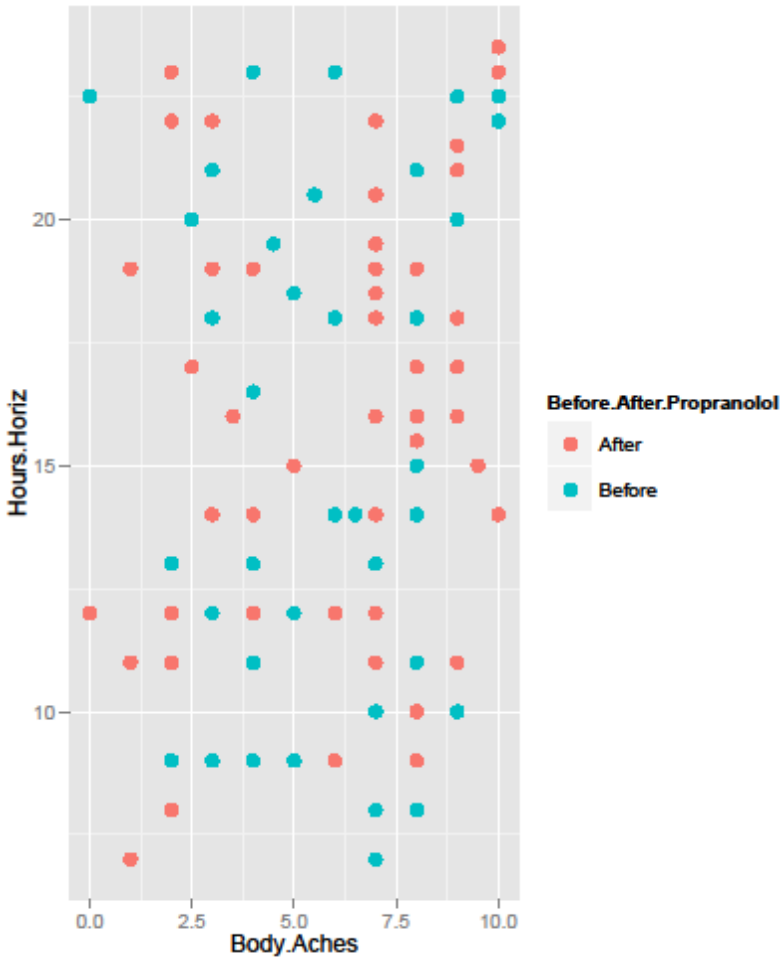


Figure 19. Scatterplot comparing body aches before and after propranolol treatment to hours horizontal before and after propranolol treatment.

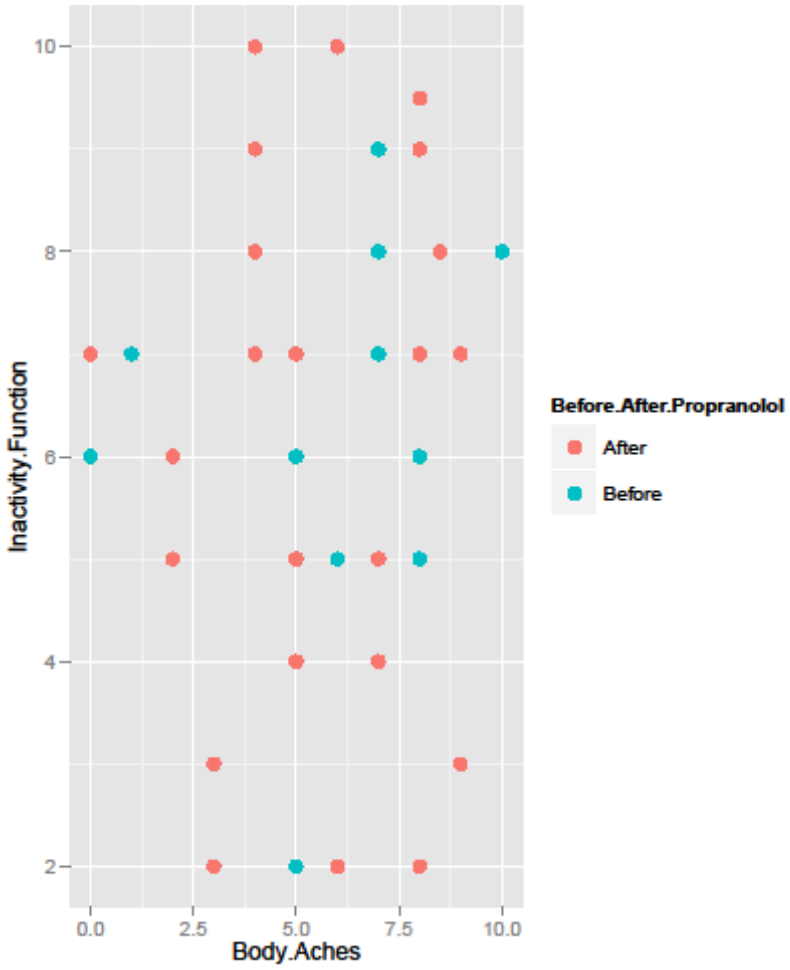


Figure 20. Scatterplot comparing body aches before and after propranolol treatment to inactivity/function before and after propranolol treatment.

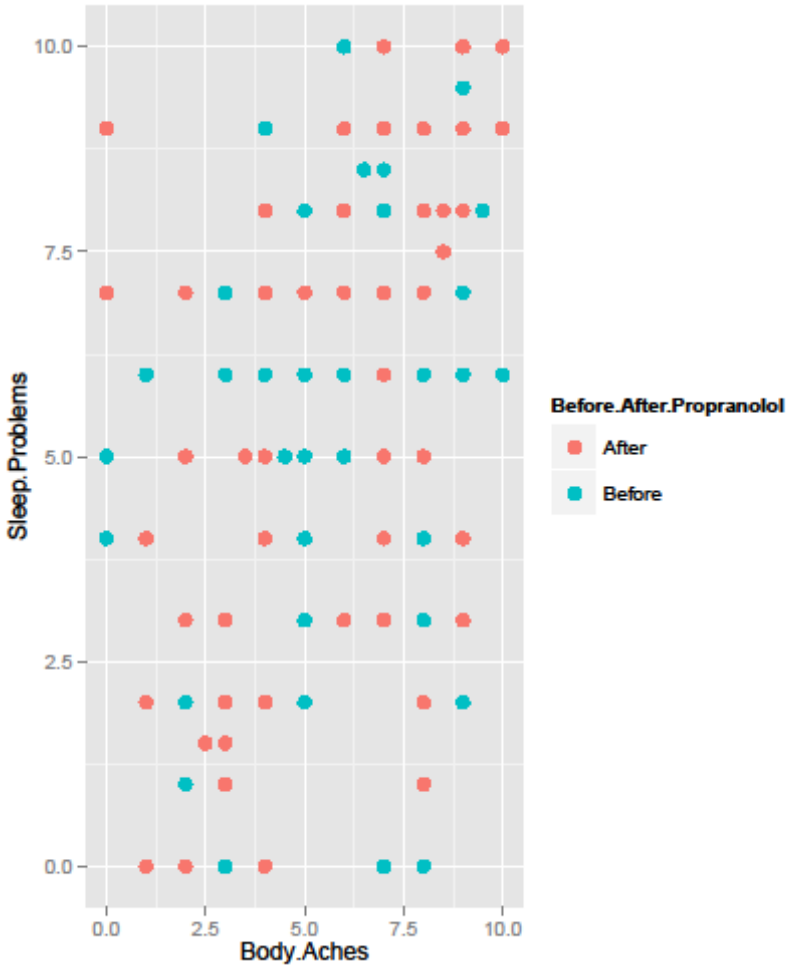


Figure 21. Scatterplot comparing body aches before and after propranolol treatment to sleep problems before and after propranolol treatment.

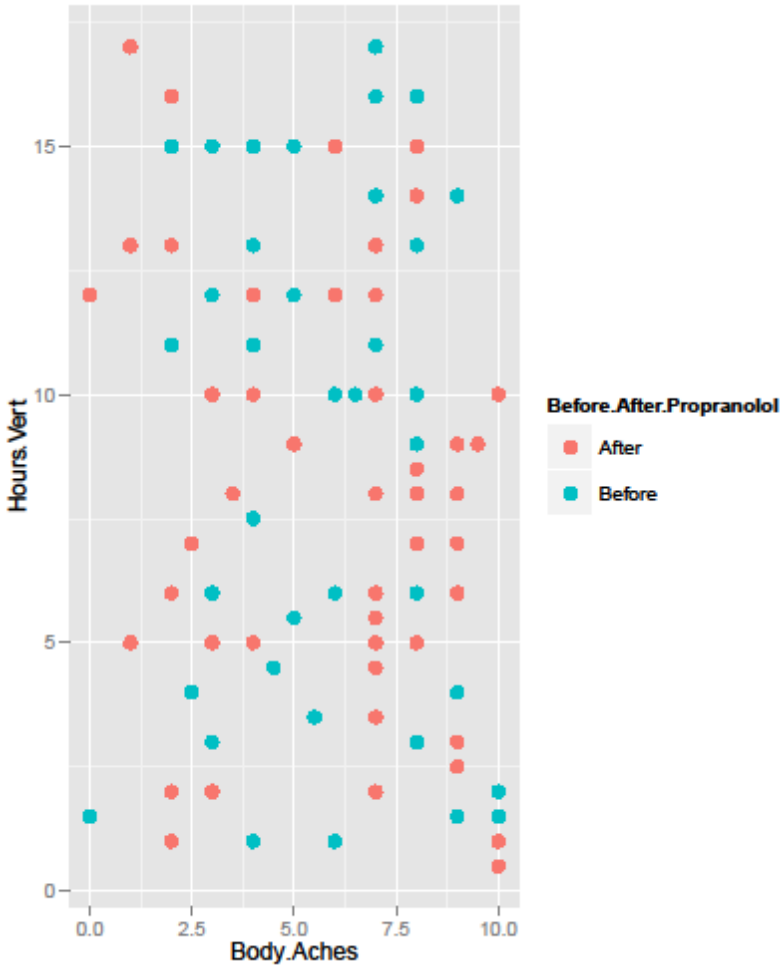


Figure 22. Scatterplot comparing body aches before and after propranolol treatment to hours vertical before and after propranolol treatment.

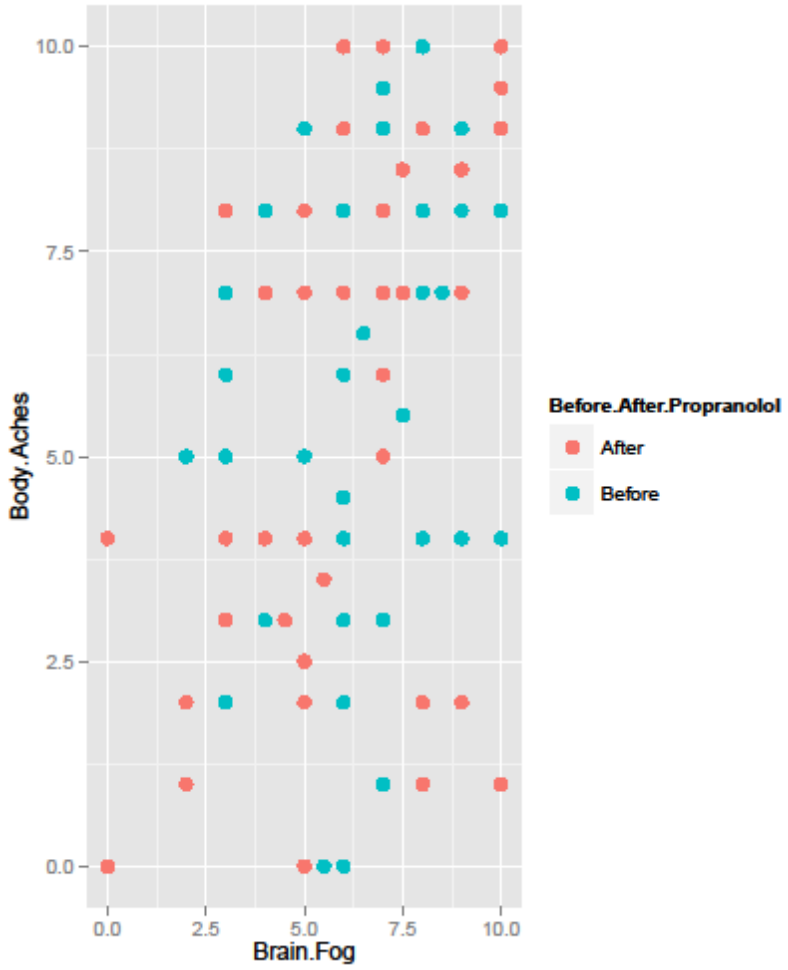


Figure 23. Scatterplot comparing brain fog before and after propranolol treatment to body aches before and after propranolol treatment.

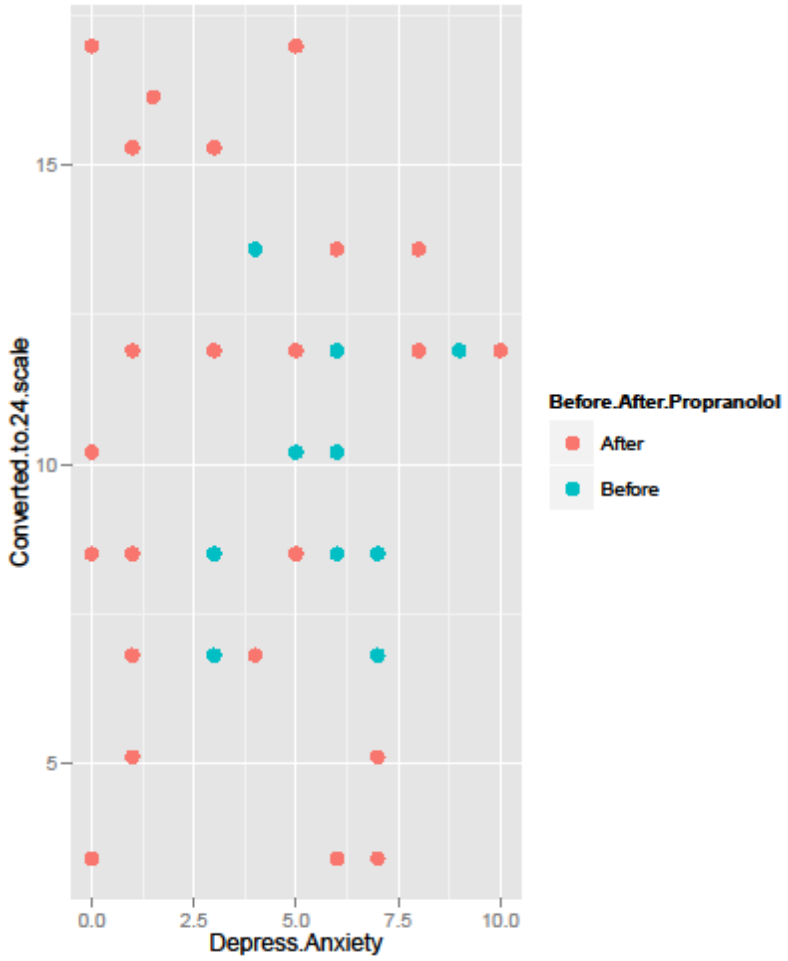


Figure 24. Scatterplot comparing depression/anxiety before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

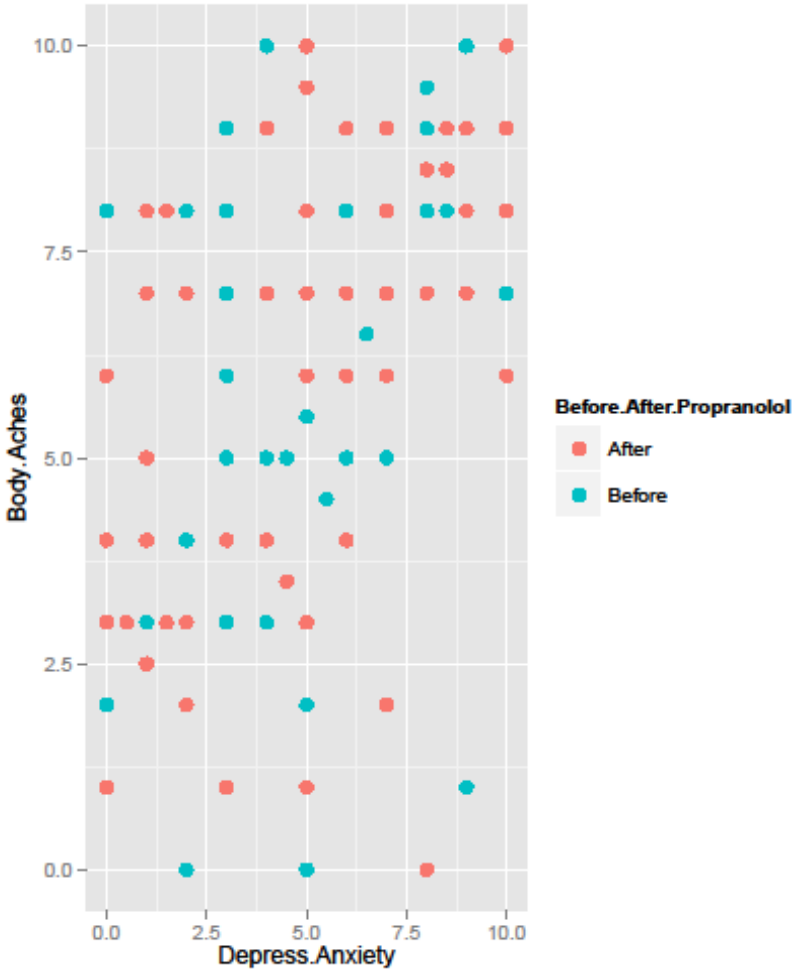


Figure 25. Scatterplot comparing depression/anxiety before and after propranolol treatment to body aches before and after propranolol treatment.

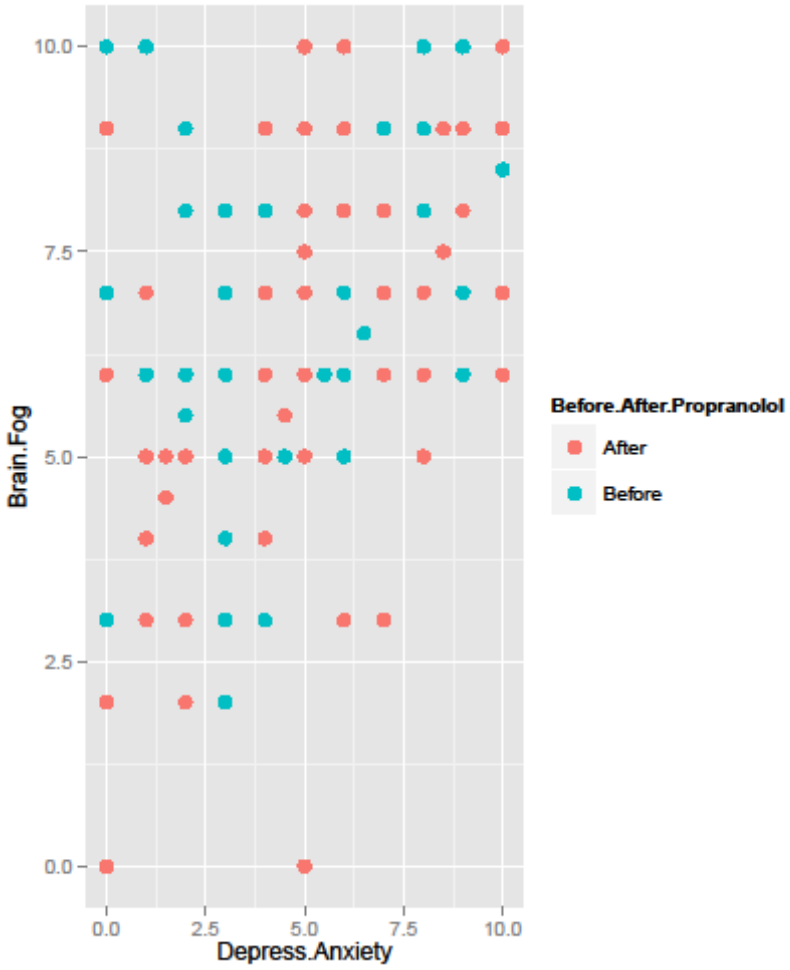


Figure 26. Scatterplot comparing depression/anxiety before and after propranolol treatment to brain fog before and after propranolol treatment.

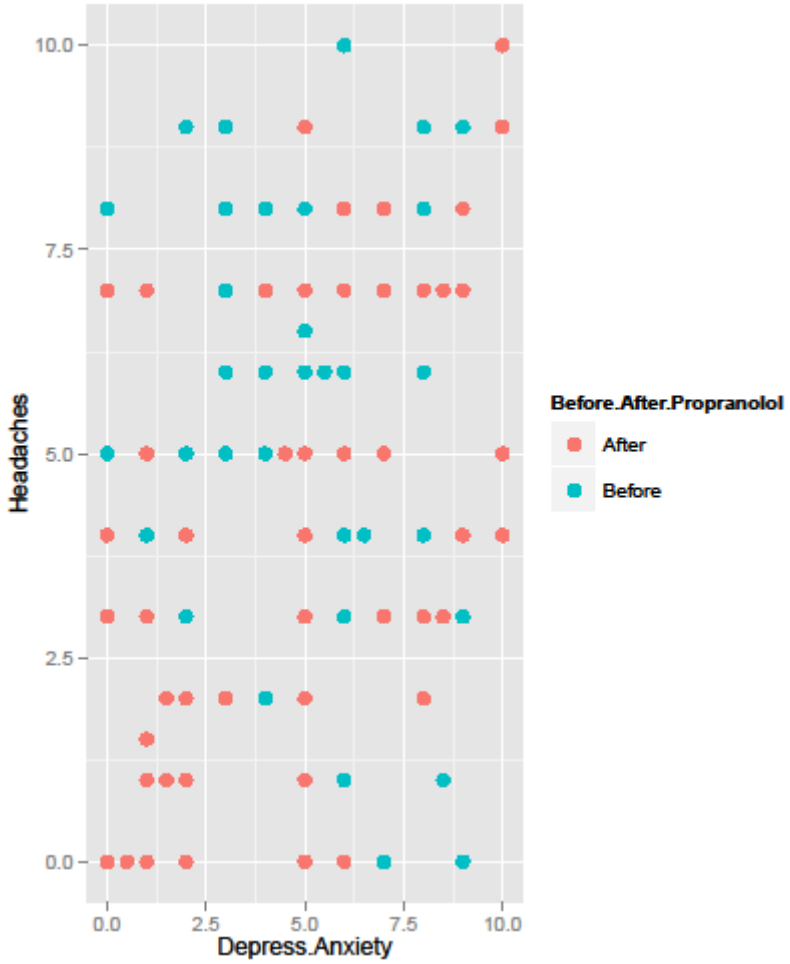


Figure 27. Scatterplot comparing depression/anxiety before and after propranolol treatment to headaches before and after propranolol treatment.

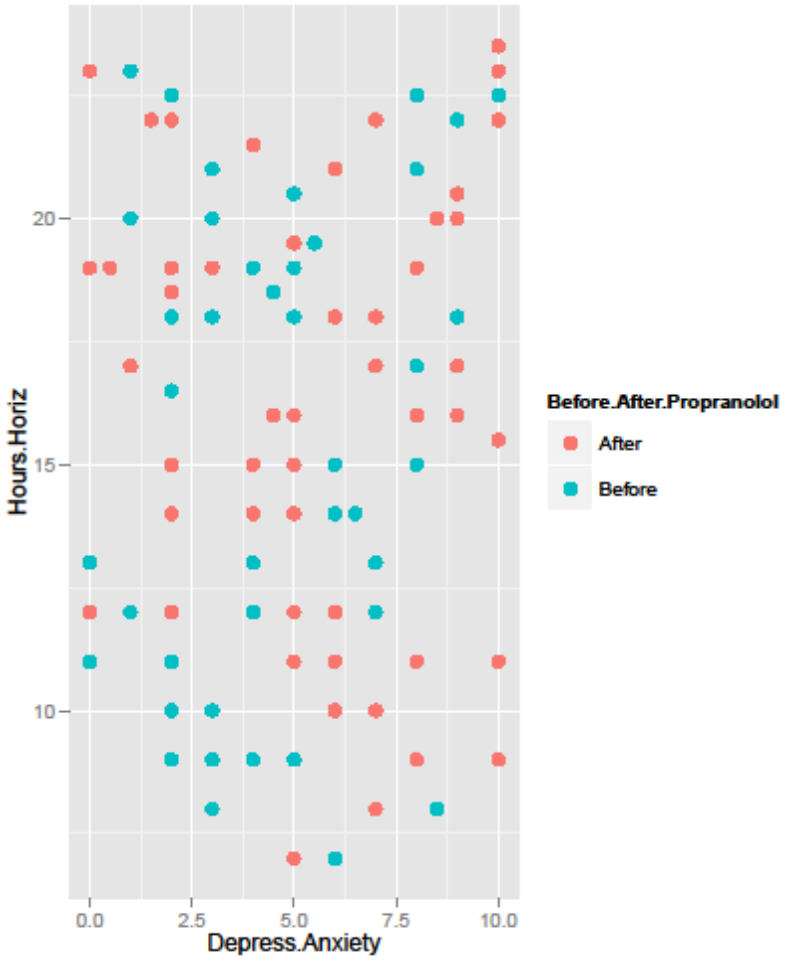


Figure 28. Scatterplot comparing depression/anxiety before and after propranolol treatment to hours horizontal before and after propranolol treatment.

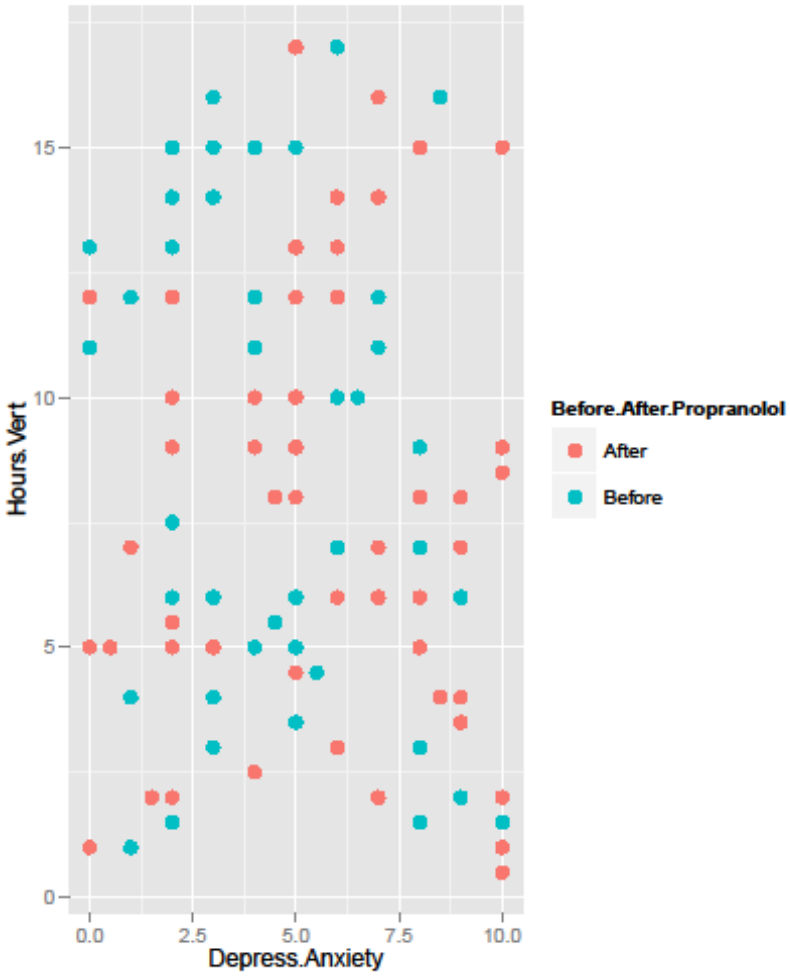


Figure 29. Scatterplot comparing depression/anxiety before and after propranolol treatment to hours vertical before and after propranolol treatment.

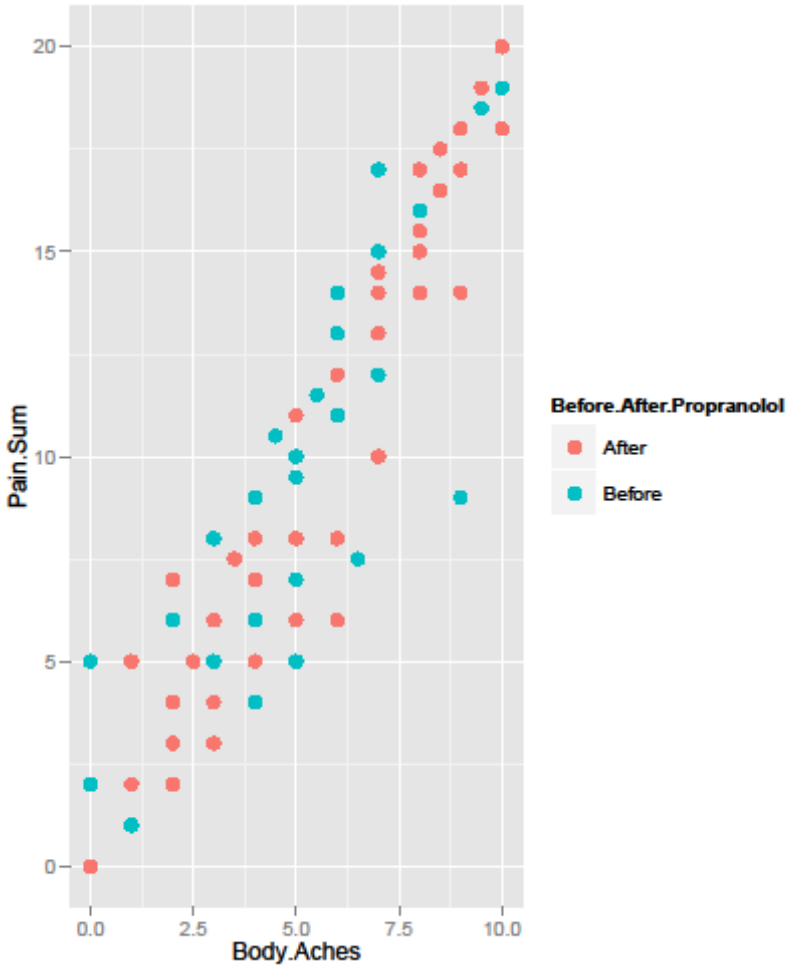


Figure 30. Scatterplot comparing body aches before and after propranolol treatment to hours pain sum before and after propranolol treatment.

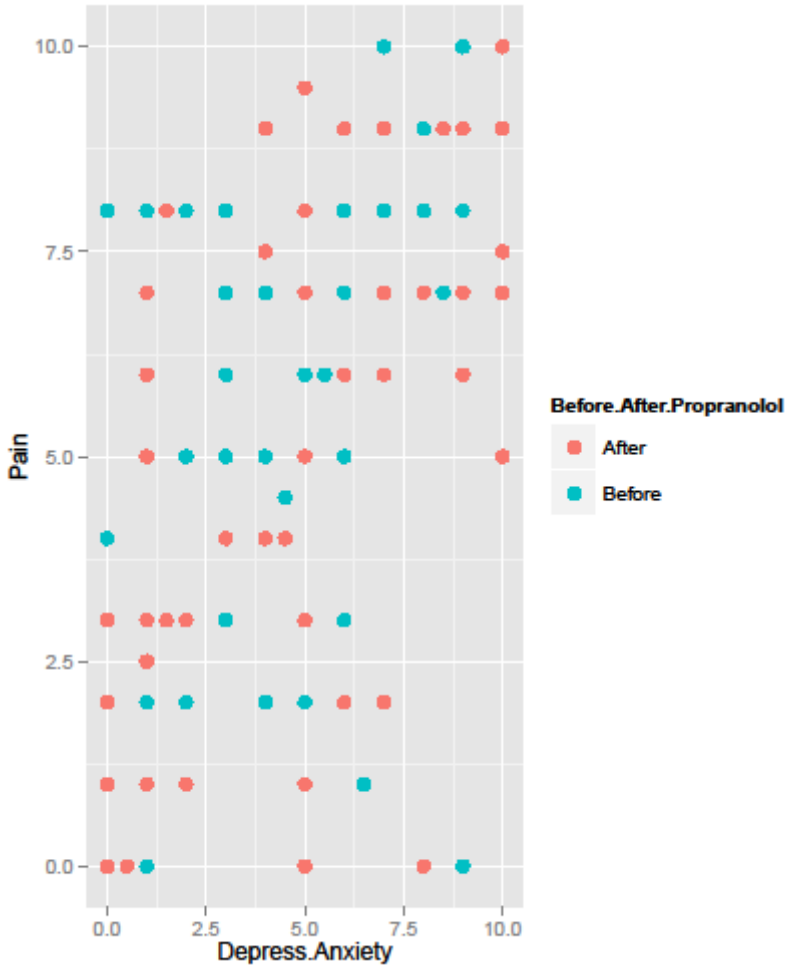


Figure 31. Scatterplot comparing depression/anxiety before and after propranolol treatment to pain before and after propranolol treatment.

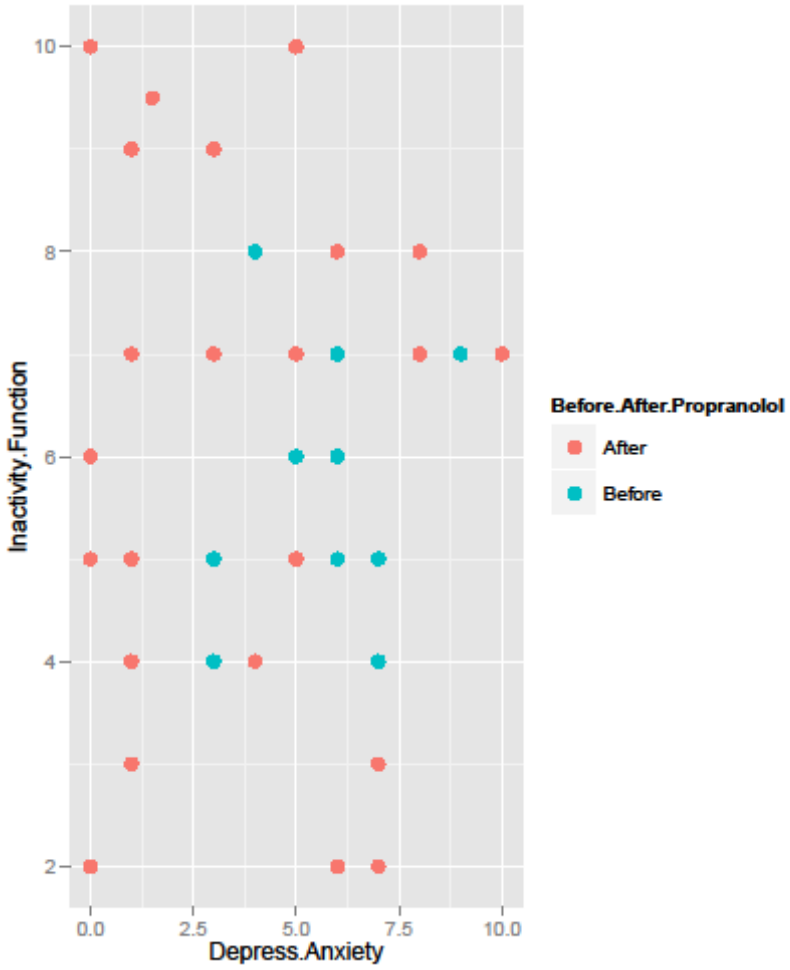


Figure 32. Scatterplot comparing depression/anxiety before and after propranolol treatment to inactivity/function before and after propranolol treatment.

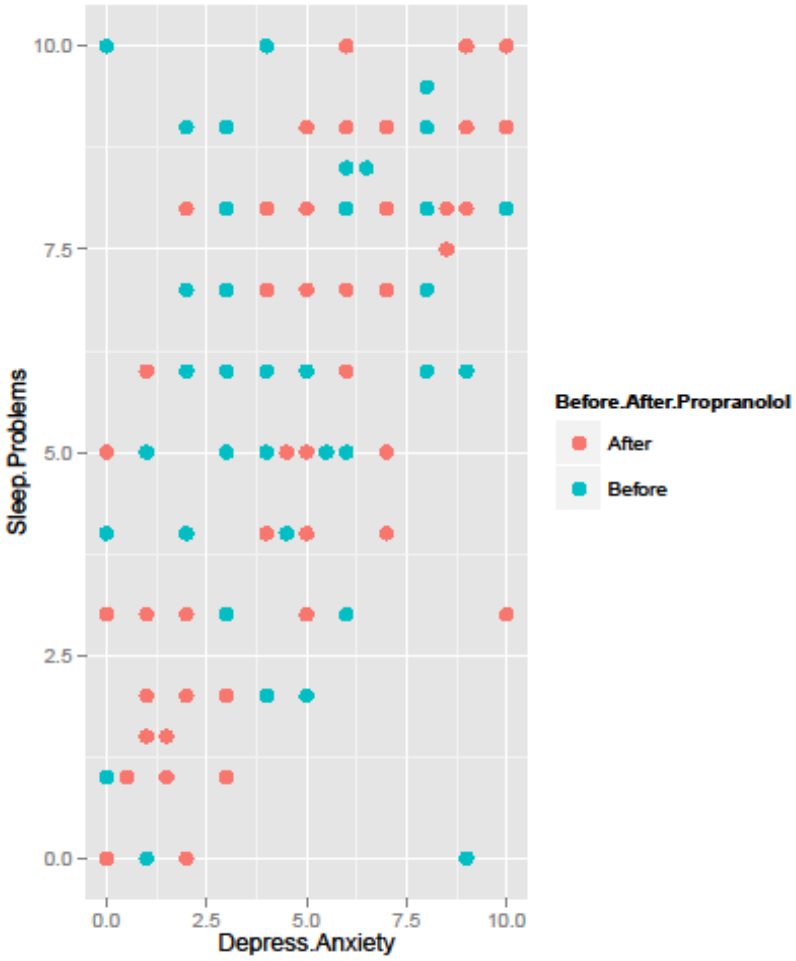


Figure 33. Scatterplot comparing depression/anxiety before and after propranolol treatment to sleep problems before and after propranolol treatment.

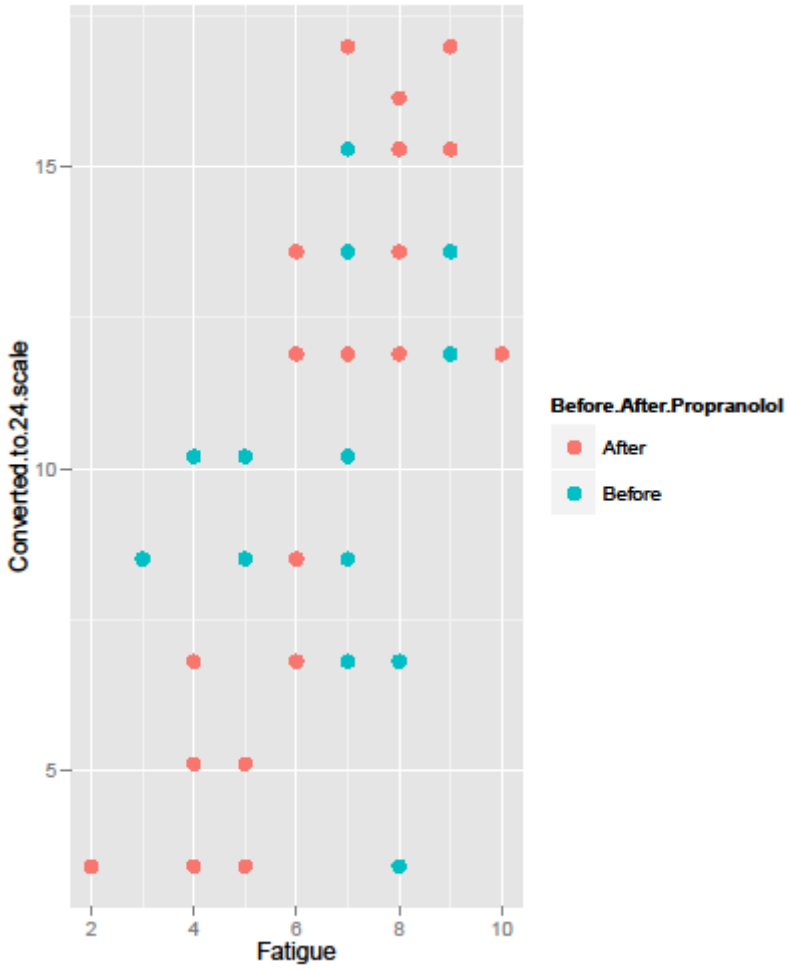


Figure 34. Scatterplot comparing fatigue before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

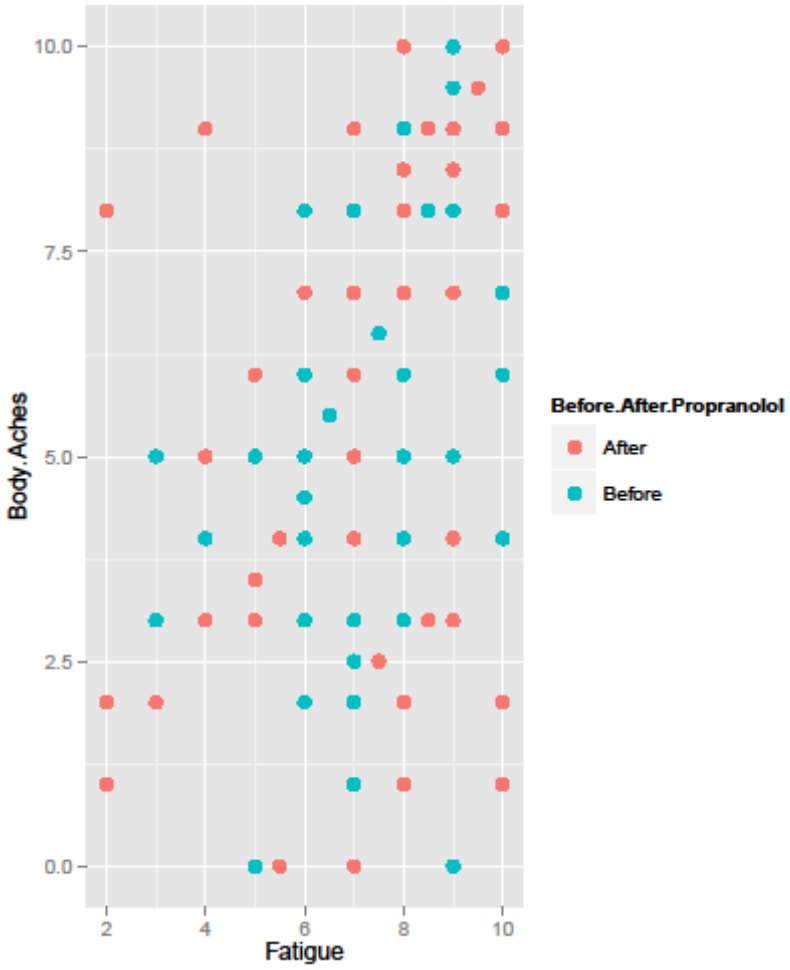


Figure 35. Scatterplot comparing fatigue before and after propranolol treatment to body aches before and after propranolol treatment.

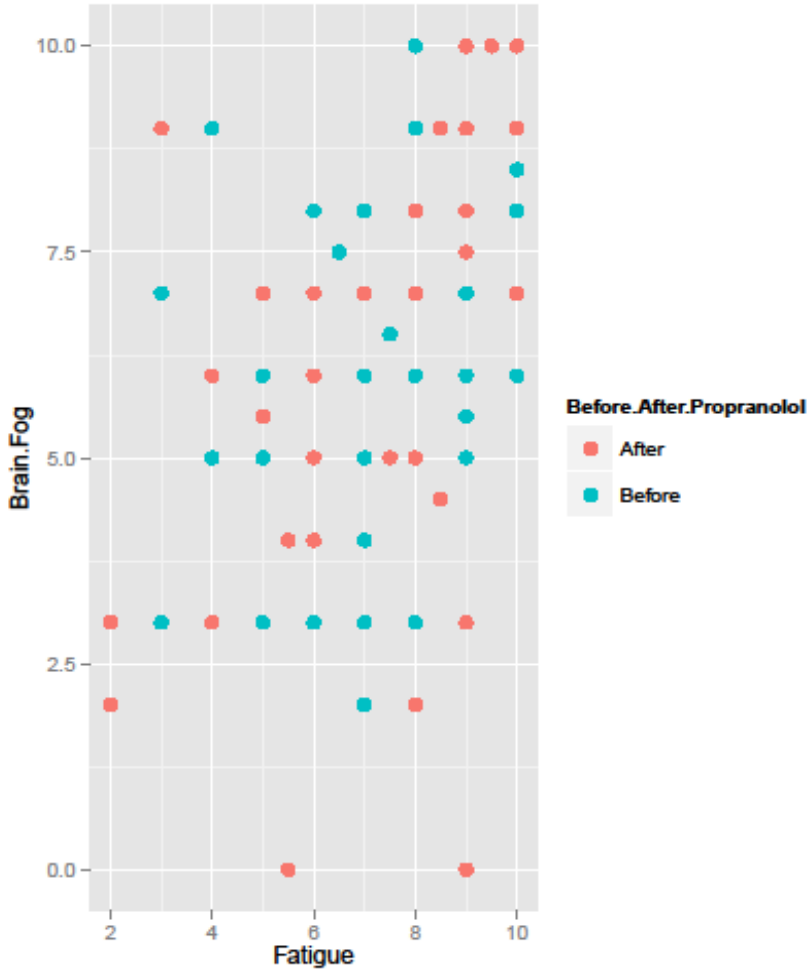


Figure 36. Scatterplot comparing fatigue before and after propranolol treatment to brain fog before and after propranolol treatment.

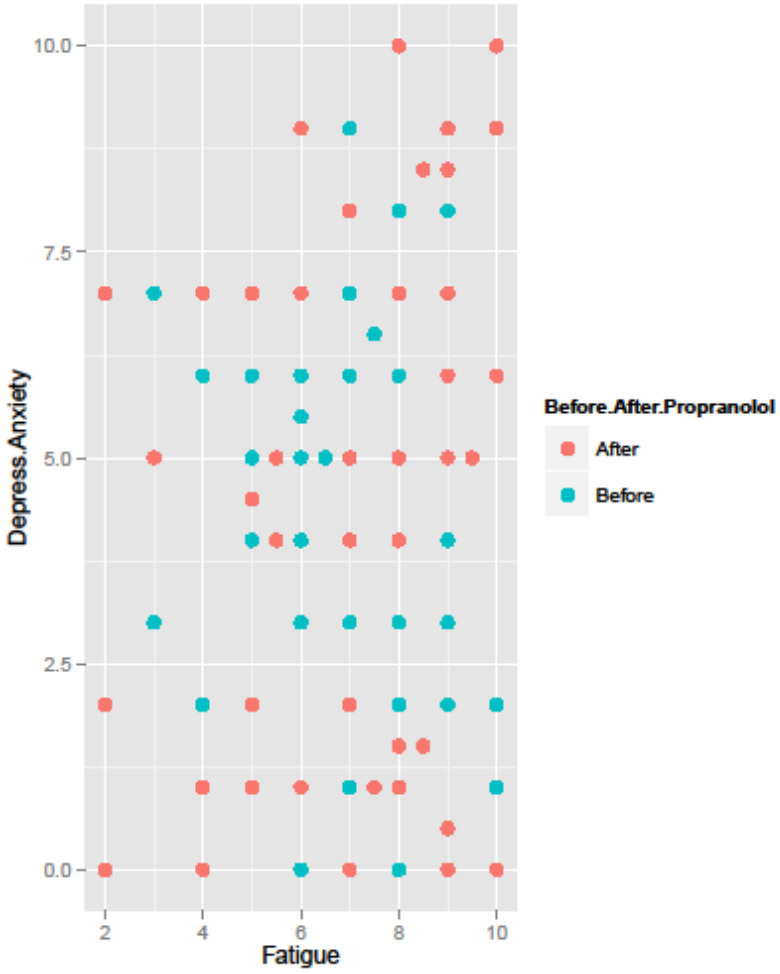


Figure 37. Scatterplot comparing fatigue before and after propranolol treatment to depression/anxiety before and after propranolol treatment.

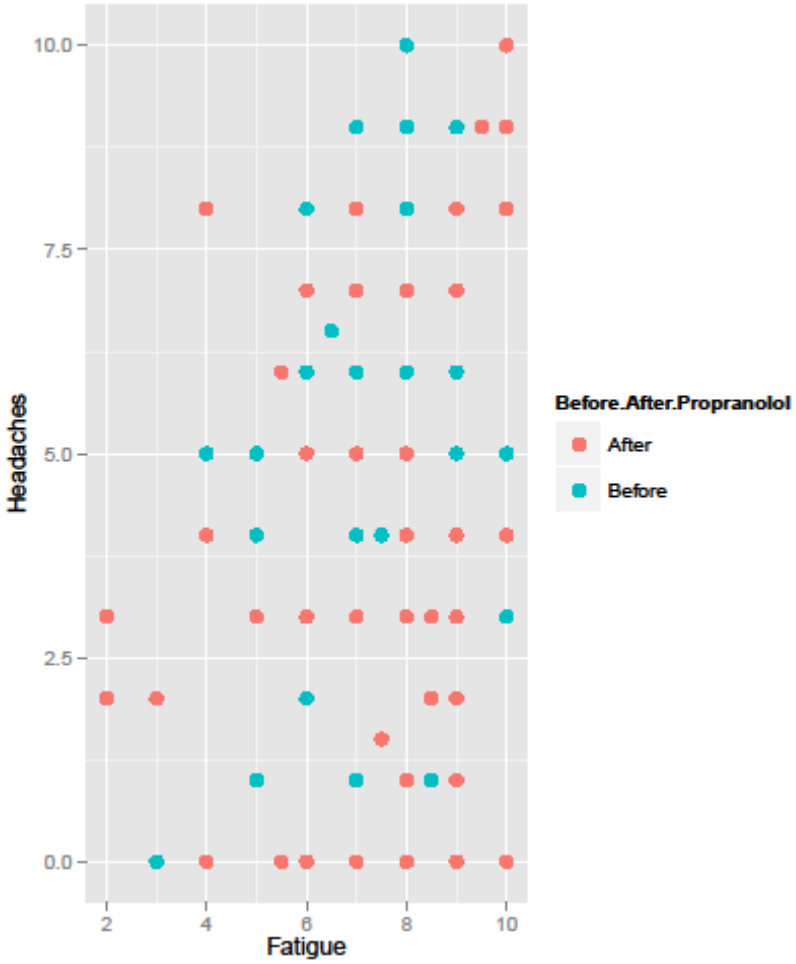


Figure 38. Scatterplot comparing fatigue before and after propranolol treatment to headaches before and after propranolol treatment.

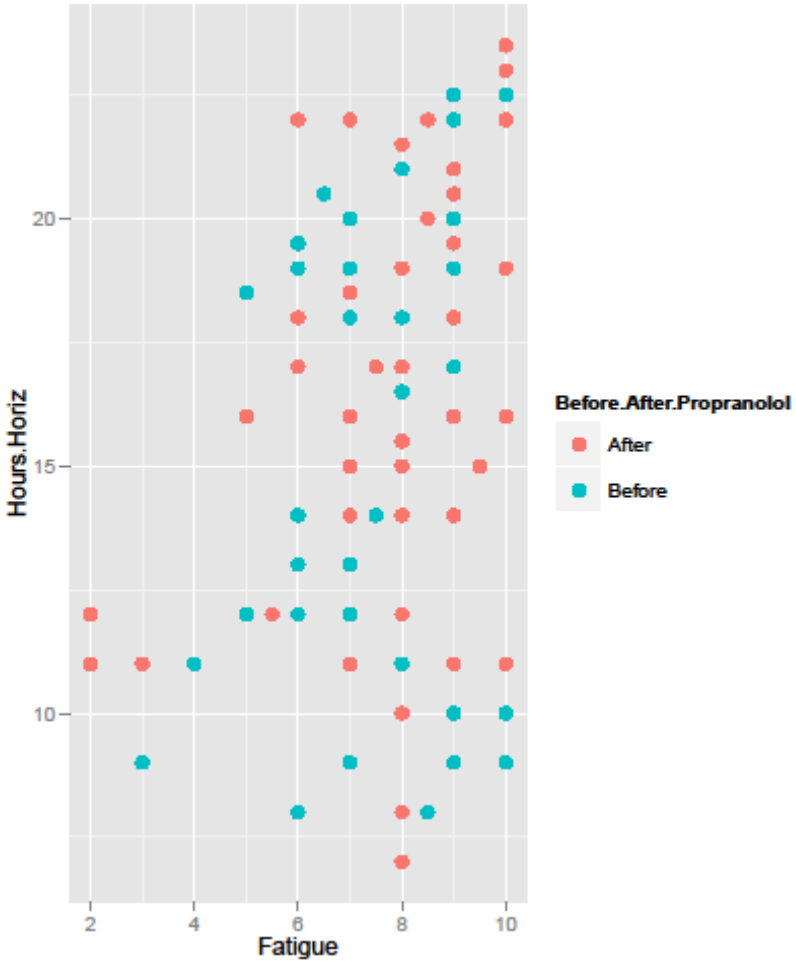


Figure 39. Scatterplot comparing fatigue before and after propranolol treatment to hours horizontal before and after propranolol treatment.

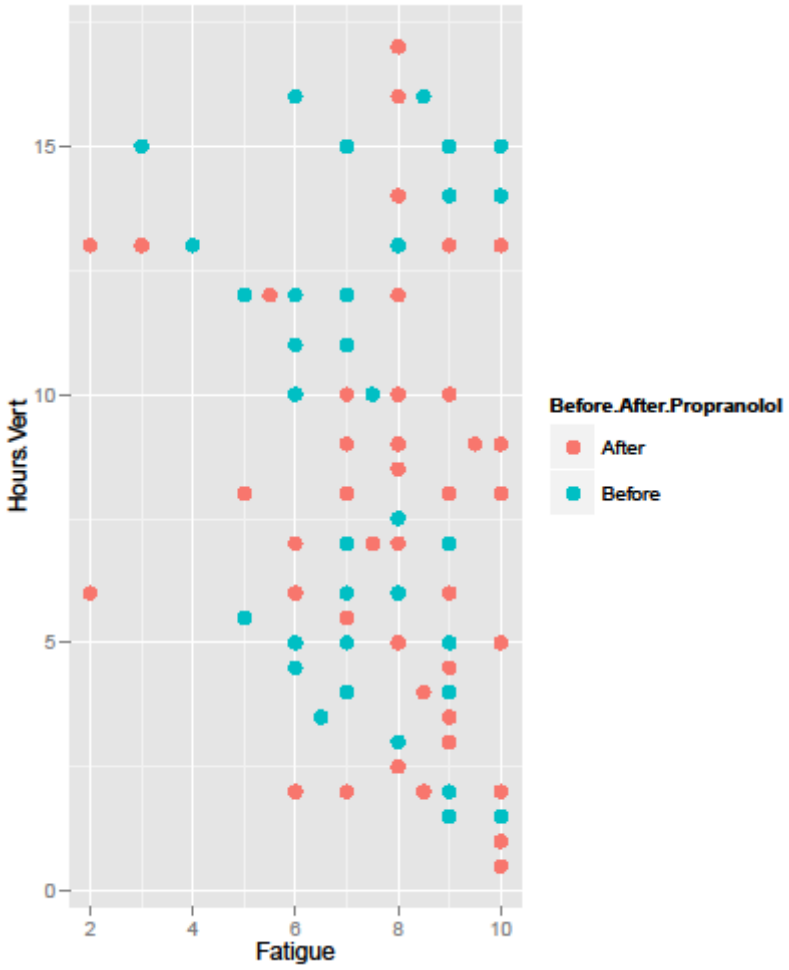


Figure 40. Scatterplot comparing fatigue before and after propranolol treatment to hours vertical before and after propranolol treatment.

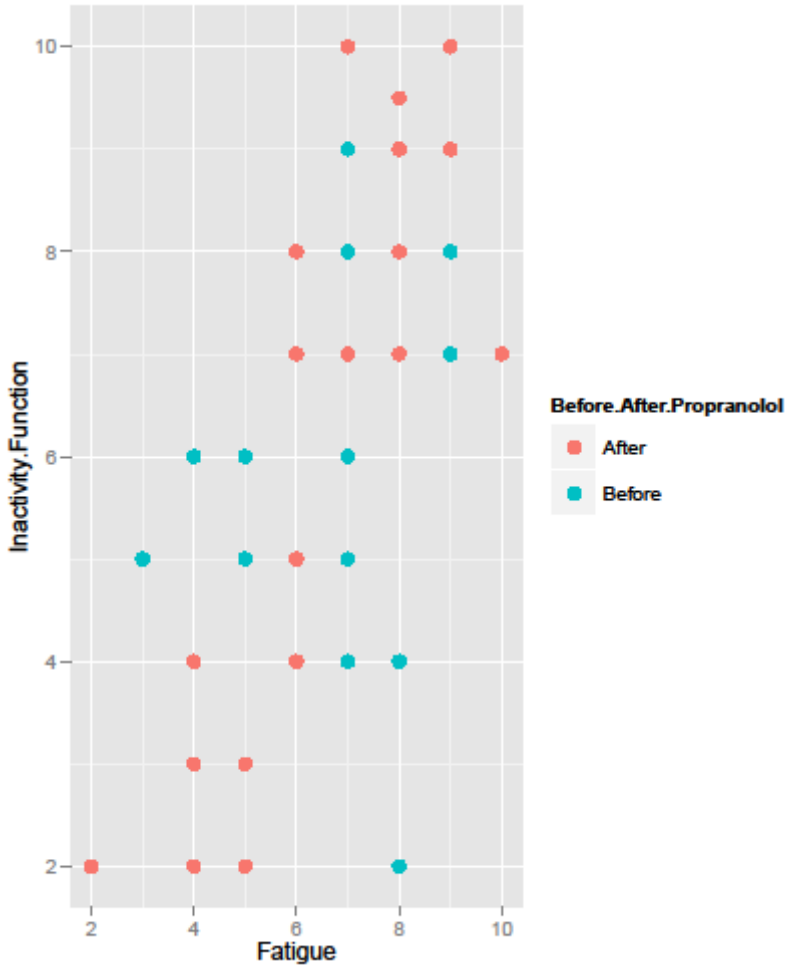


Figure 41. Scatterplot comparing fatigue before and after propranolol treatment to inactivity/function before and after propranolol treatment.

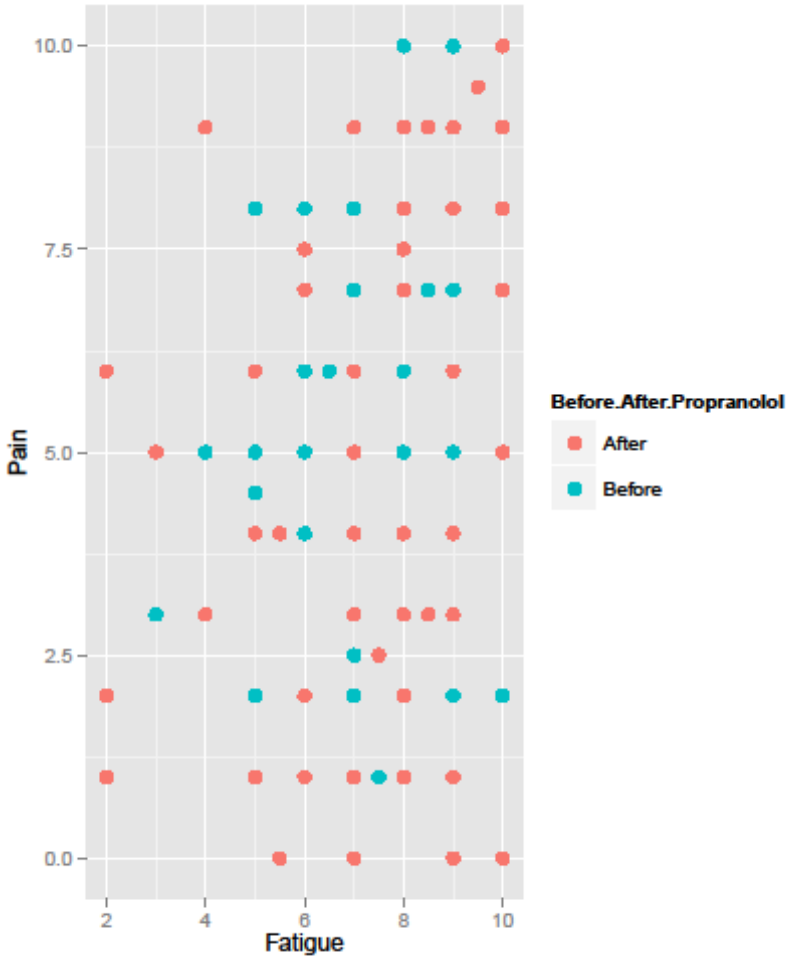


Figure 42. Scatterplot comparing fatigue before and after propranolol treatment to pain before and after propranolol treatment.

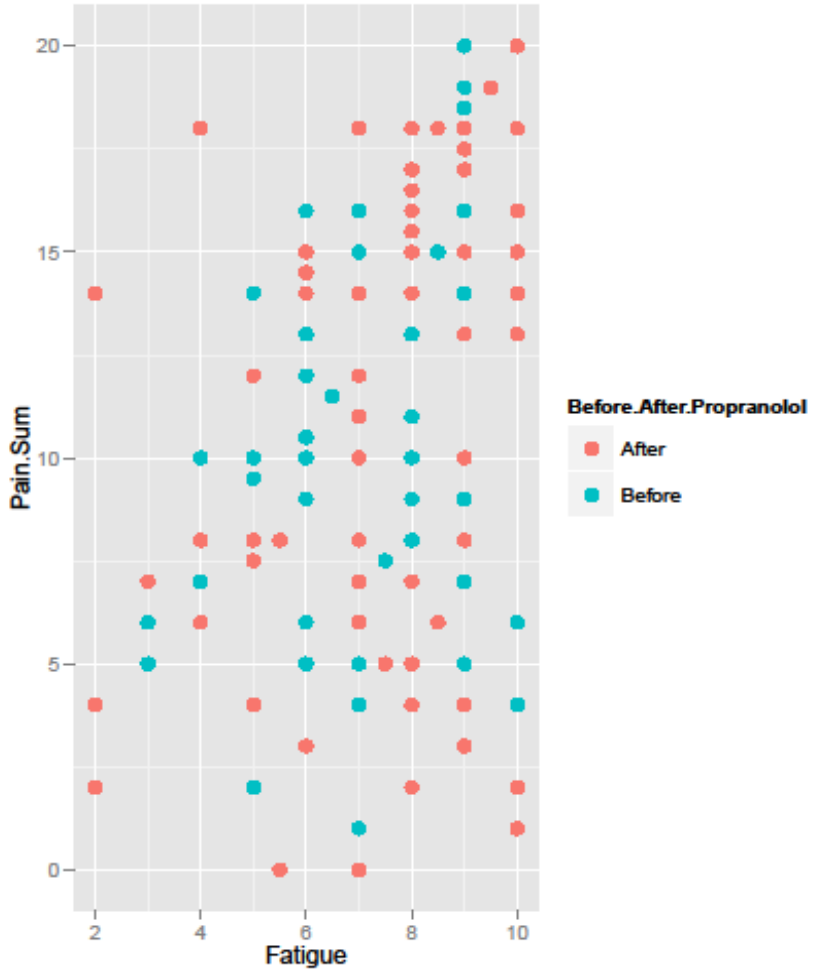


Figure 43. Scatterplot comparing fatigue before and after propranolol treatment to pain sum before and after propranolol treatment.

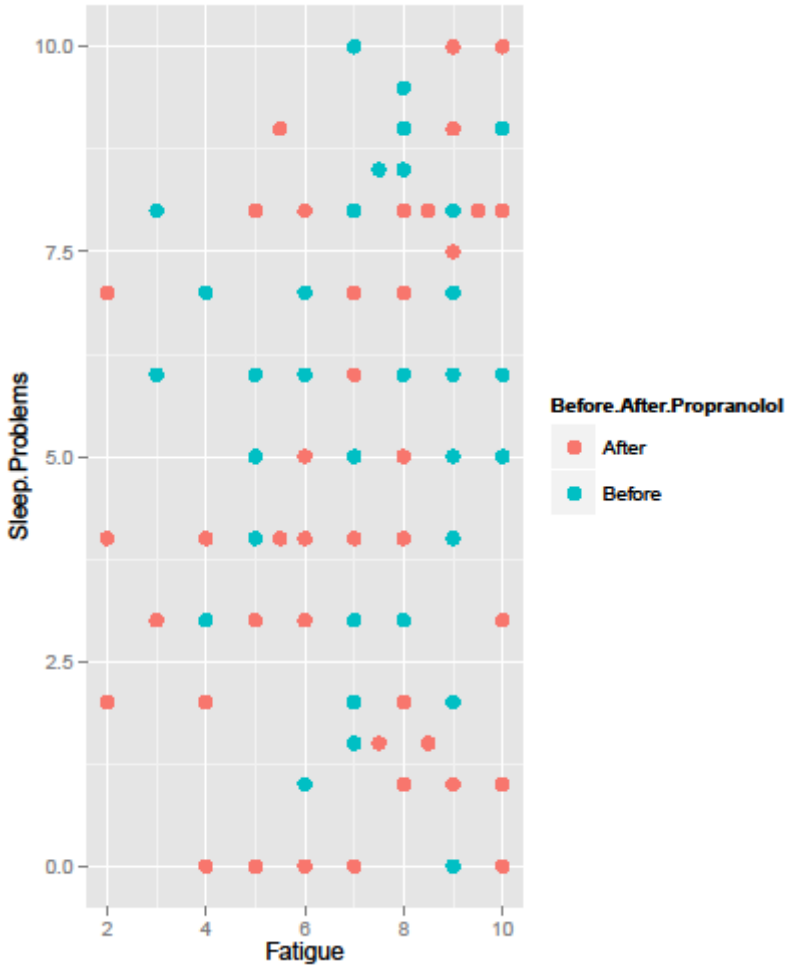


Figure 44. Scatterplot comparing fatigue before and after propranolol treatment to sleep problems before and after propranolol treatment.

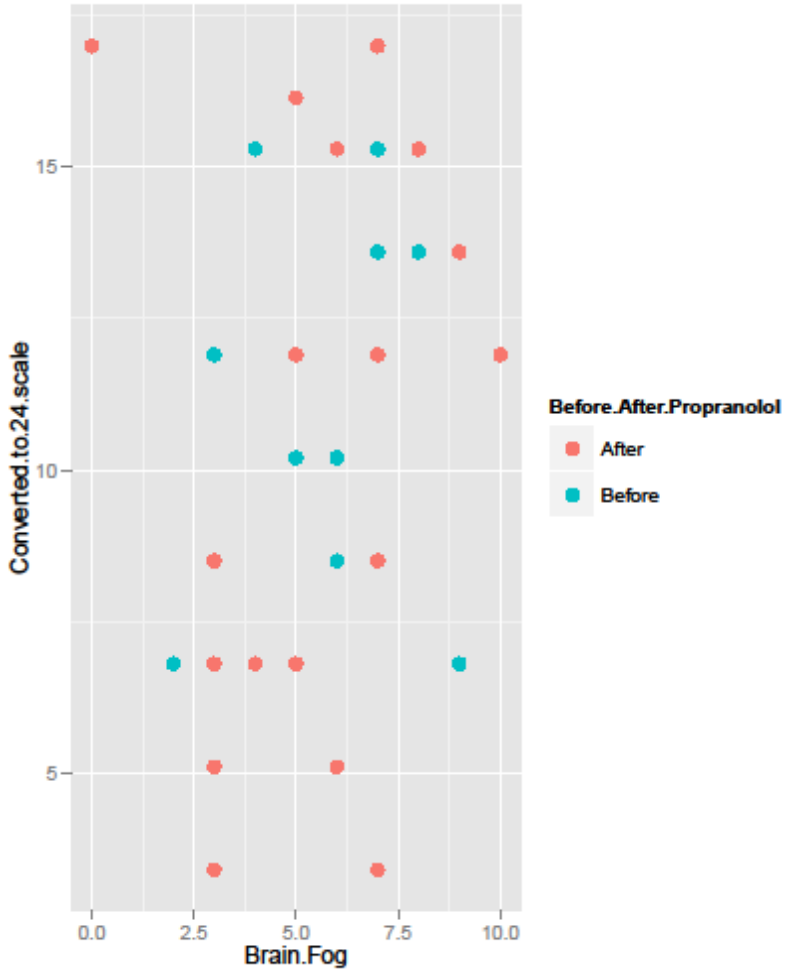


Figure 45. Scatterplot comparing brain fog before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

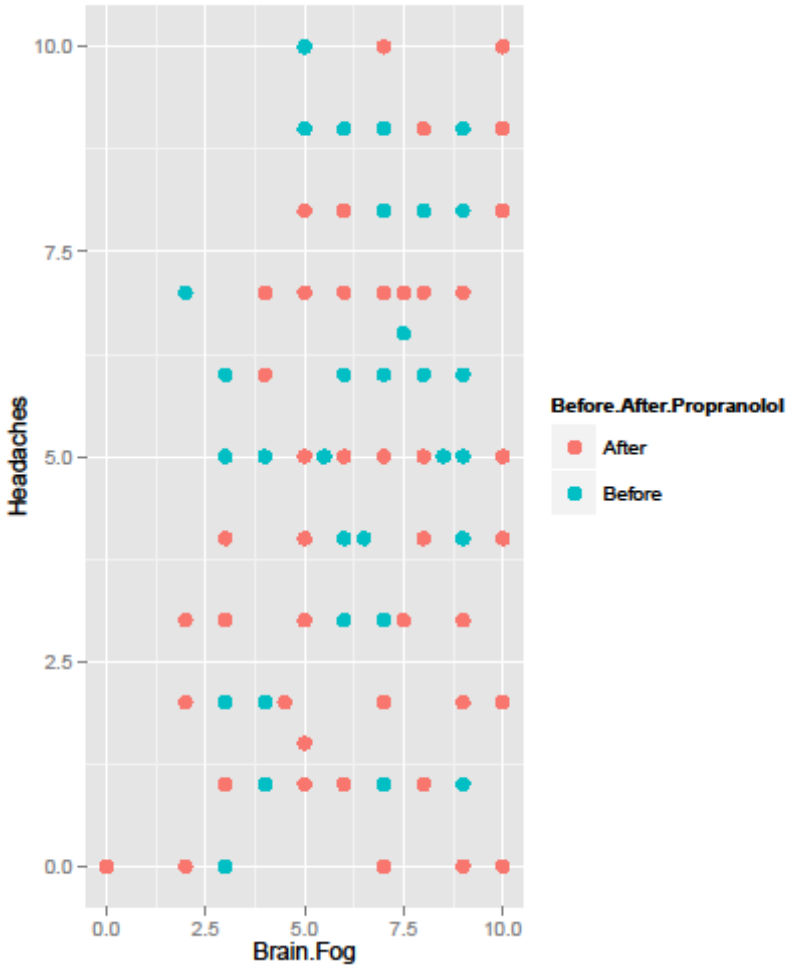


Figure 46. Scatterplot comparing brain fog before and after propranolol treatment to headaches before and after propranolol treatment.

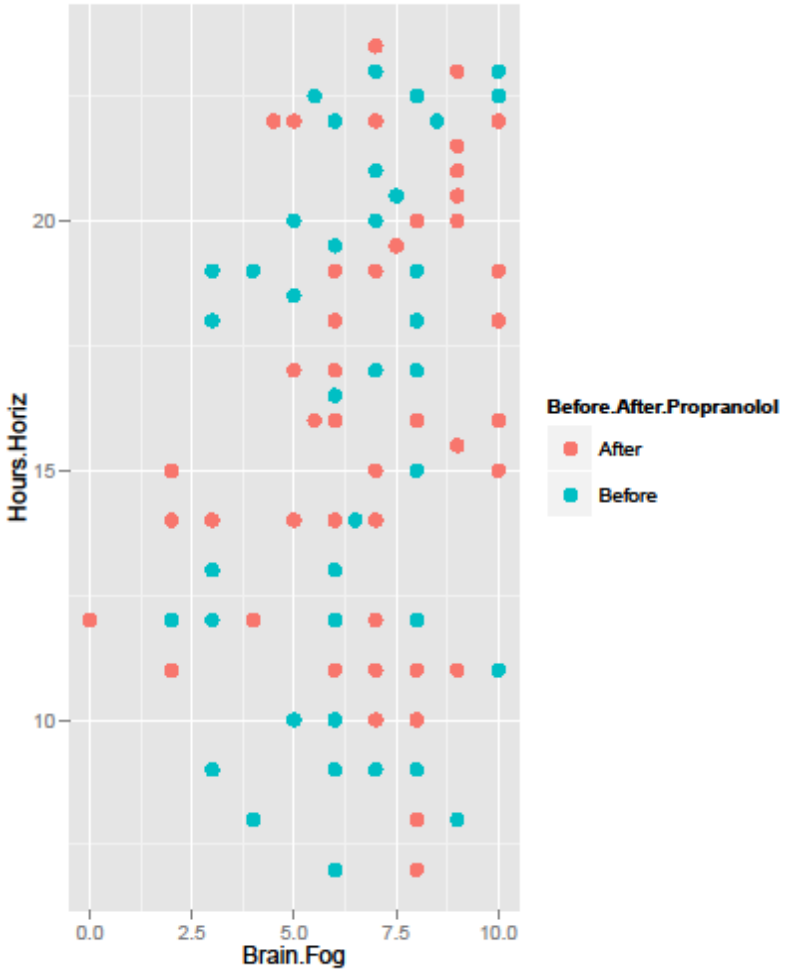


Figure 47. Scatterplot comparing brain fog before and after propranolol treatment to hours horizontal before and after propranolol treatment.

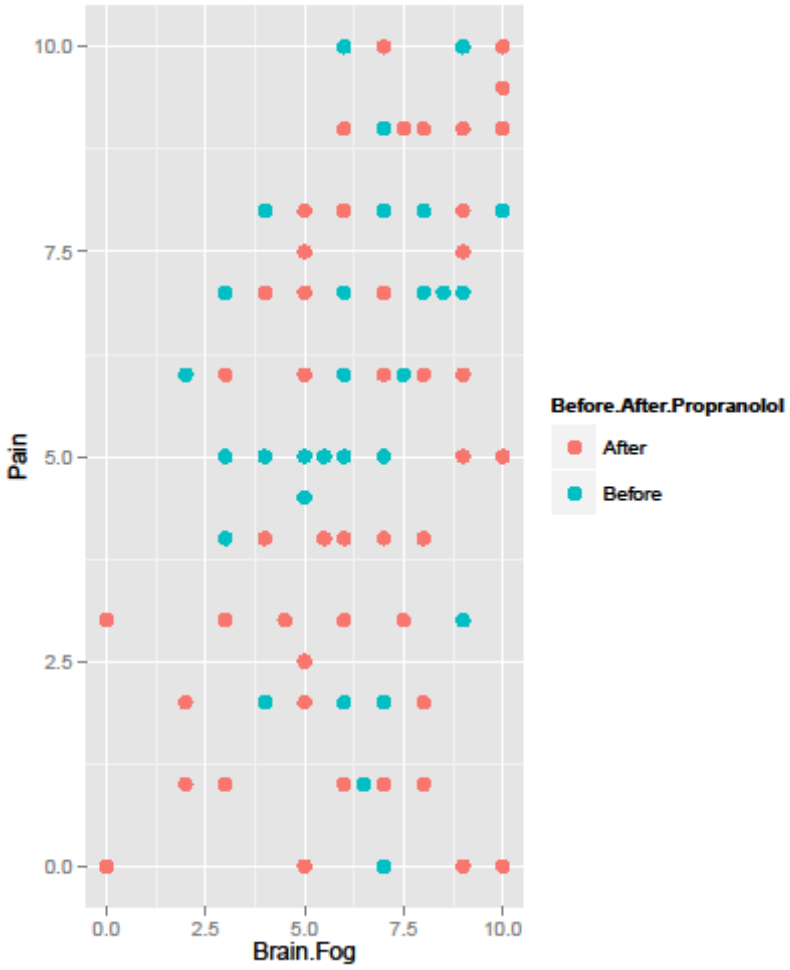


Figure 48. Scatterplot comparing brain fog before and after propranolol treatment to pain before and after propranolol treatment.

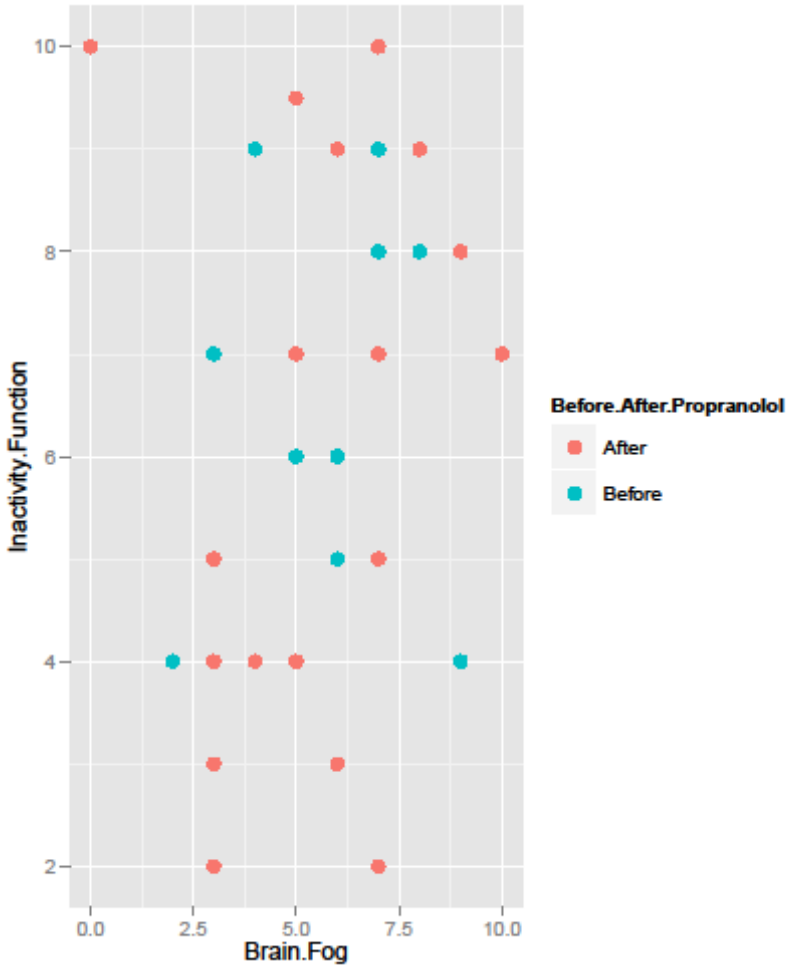


Figure 49. Scatterplot comparing brain fog before and after propranolol treatment to inactivity/function before and after propranolol treatment.

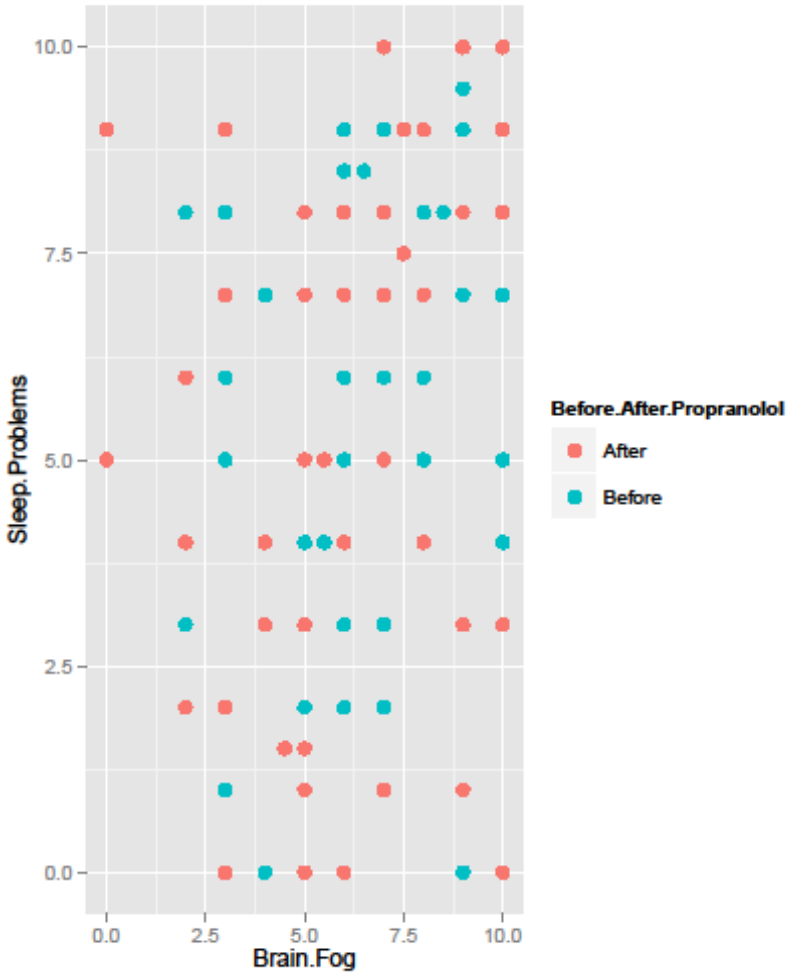


Figure 50. Scatterplot comparing brain fog before and after propranolol treatment to sleep problems before and after propranolol treatment.

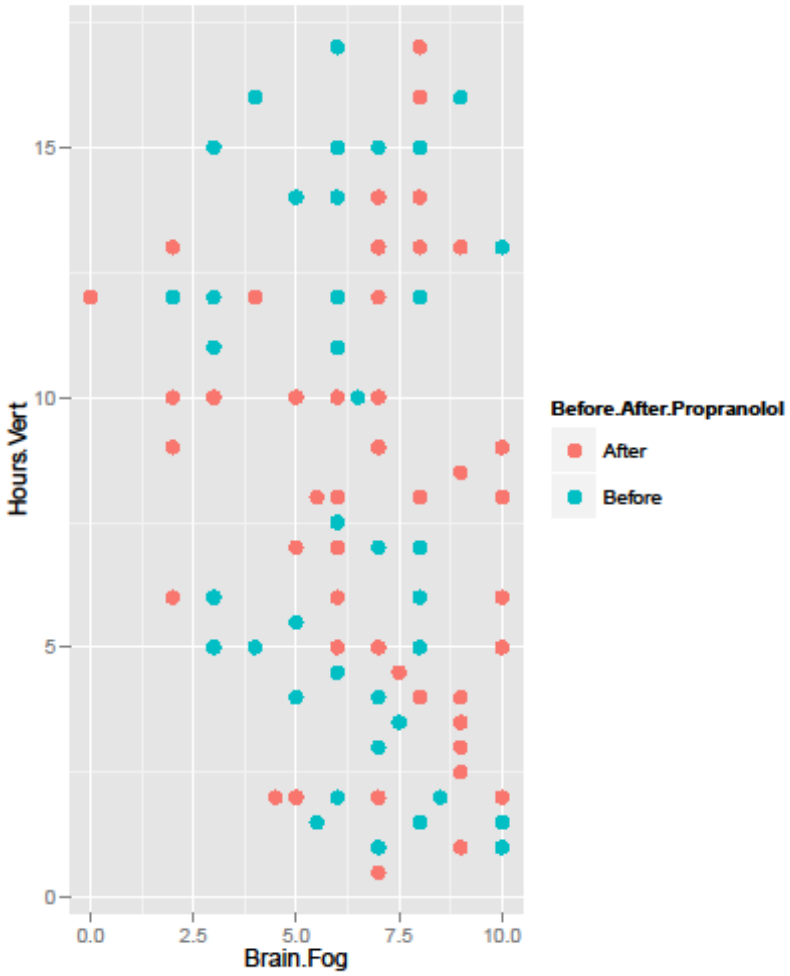


Figure 51. Scatterplot comparing brain fog before and after propranolol treatment to hours vertical before and after propranolol treatment.

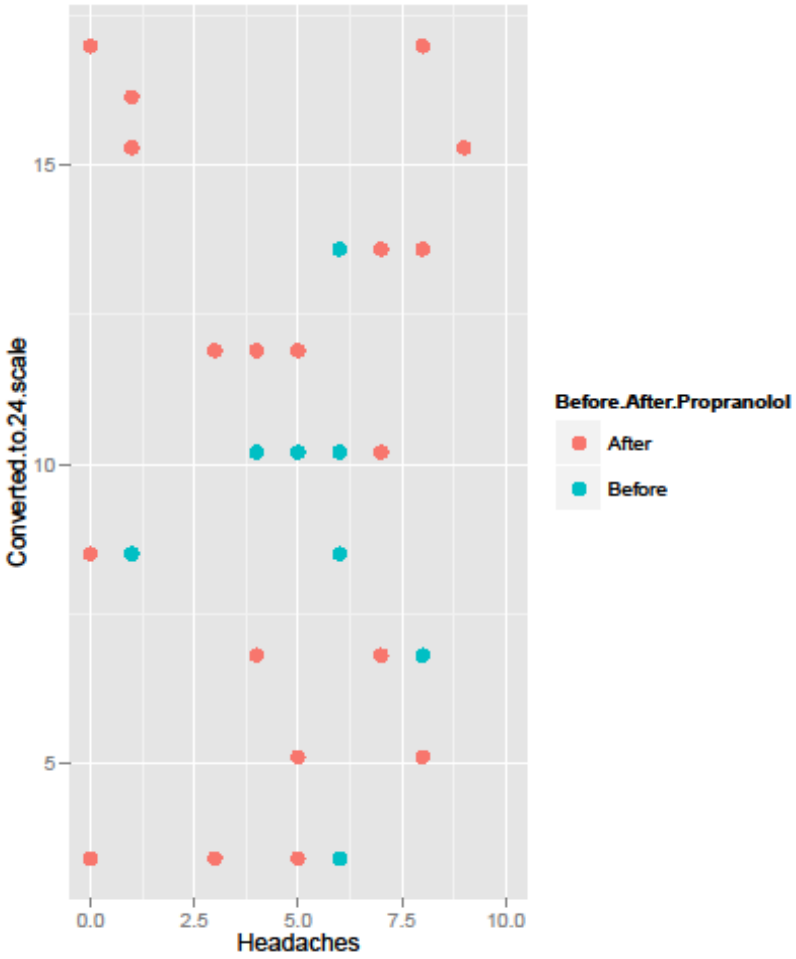


Figure 52. Scatterplot comparing headaches before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

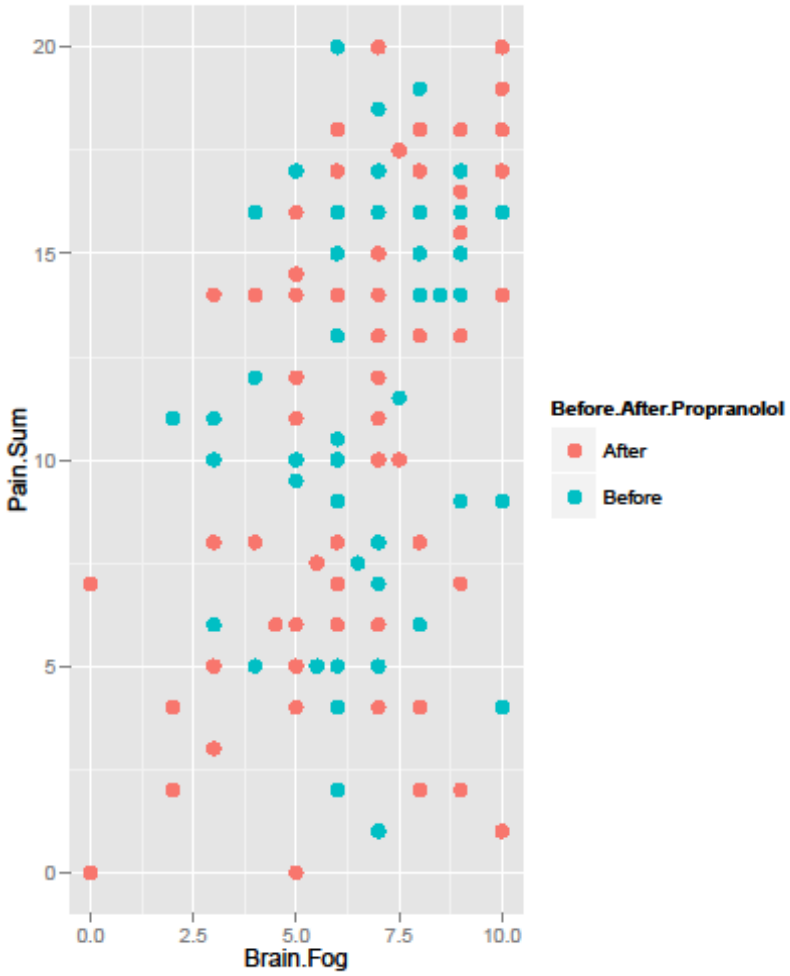


Figure 53. Scatterplot comparing brain fog before and after propranolol treatment to pain sum before and after propranolol treatment.

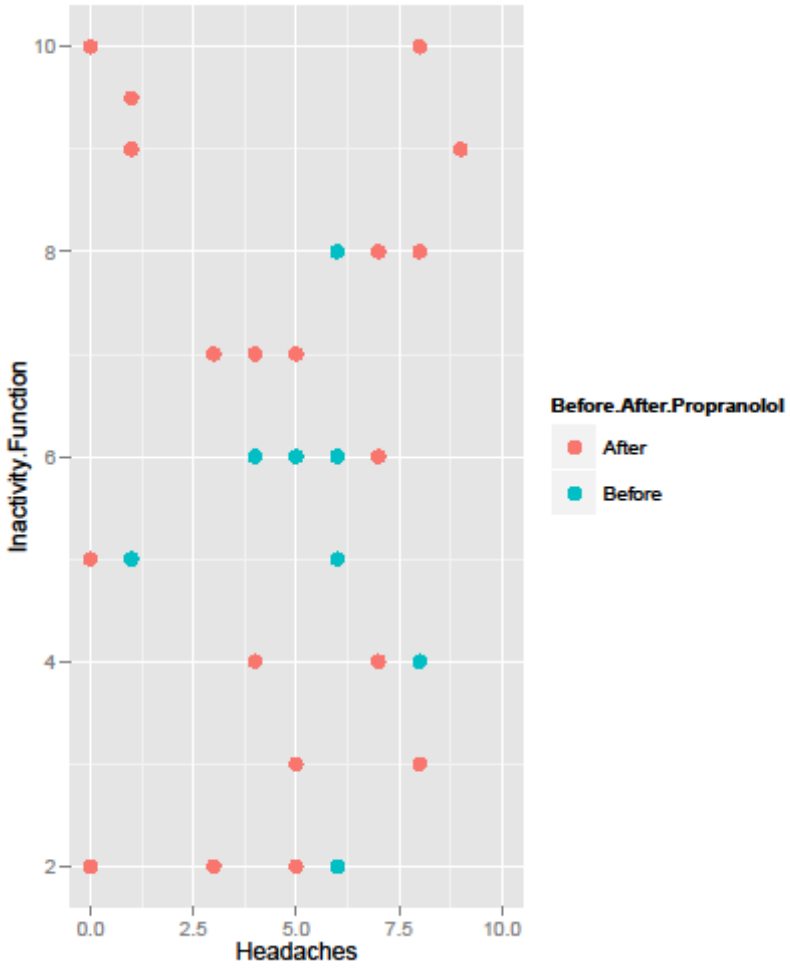


Figure 54. Scatterplot comparing headaches before and after propranolol treatment to inactivity/function before and after propranolol treatment.

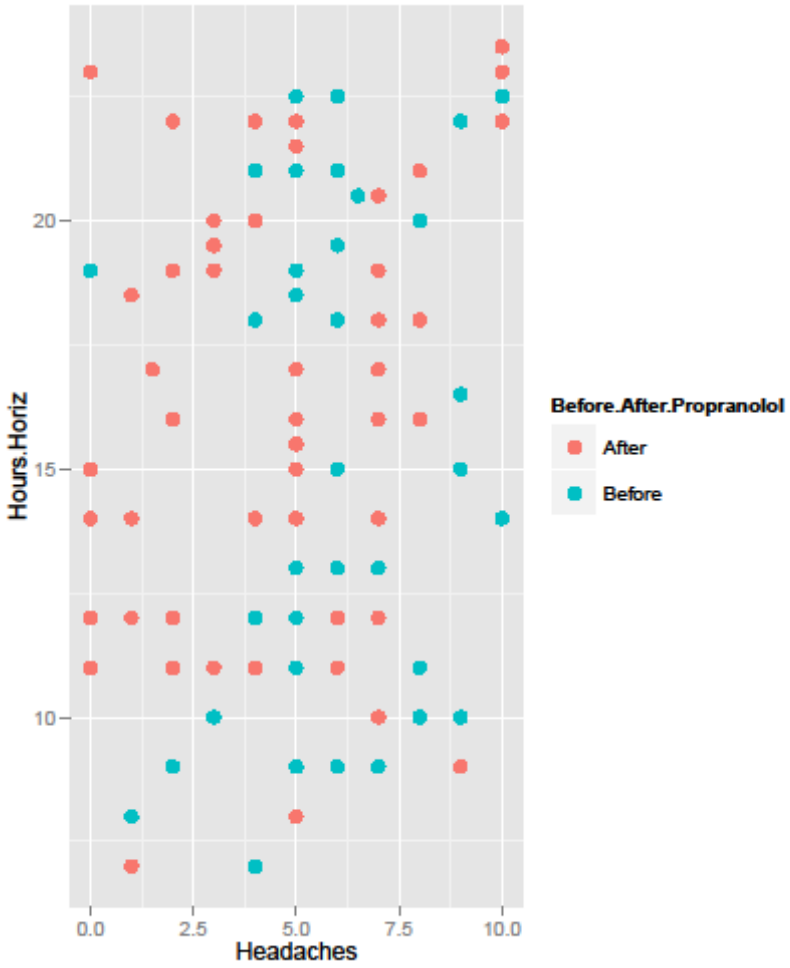


Figure 55. Scatterplot comparing headaches before and after propranolol treatment to hours horizontal before and after propranolol treatment.

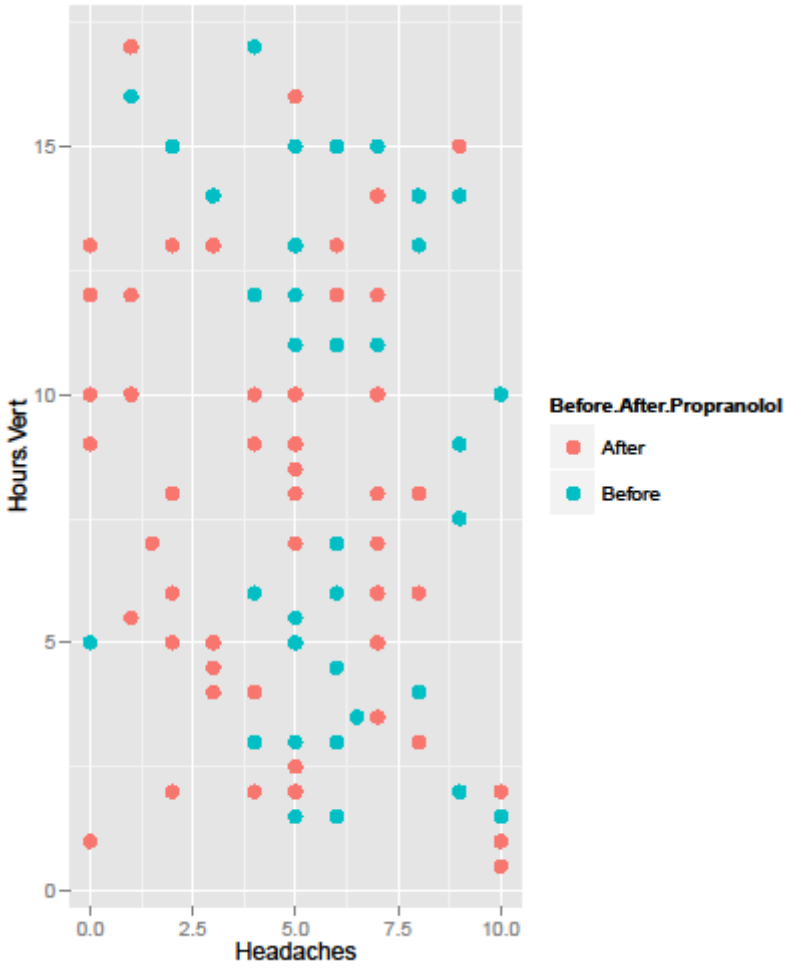


Figure 56. Scatterplot comparing headaches before and after propranolol treatment to hours vertical before and after propranolol treatment.

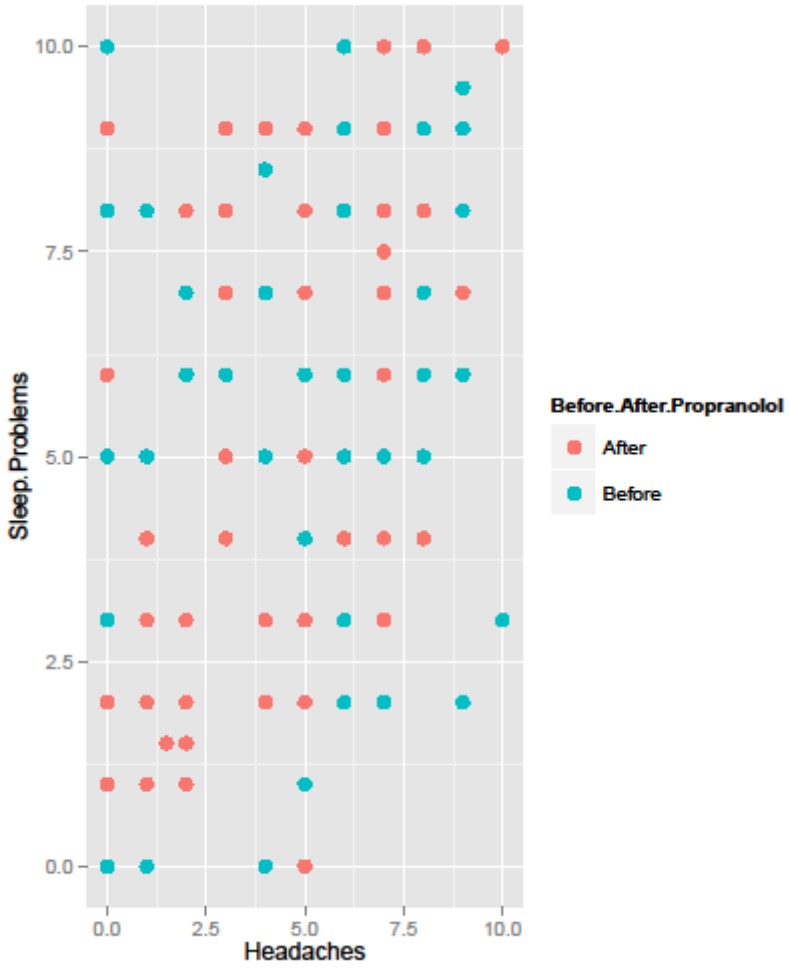


Figure 57. Scatterplot comparing headaches before and after propranolol treatment to sleep problems before and after propranolol treatment.

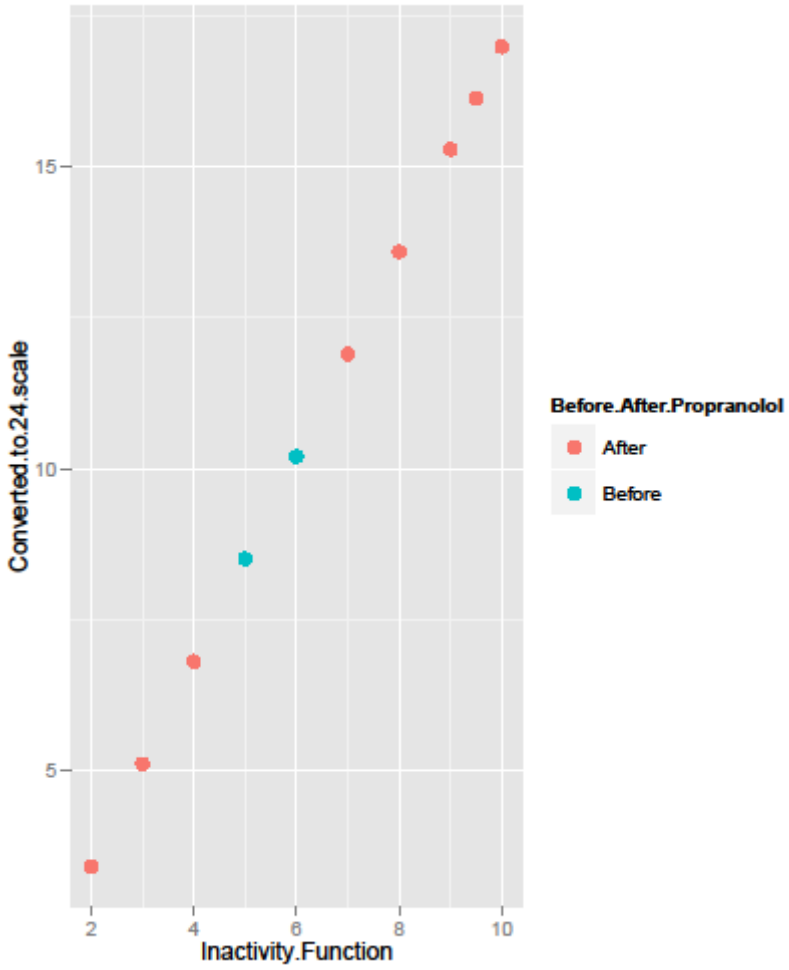


Figure 58. Scatterplot comparing inactivity/function before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

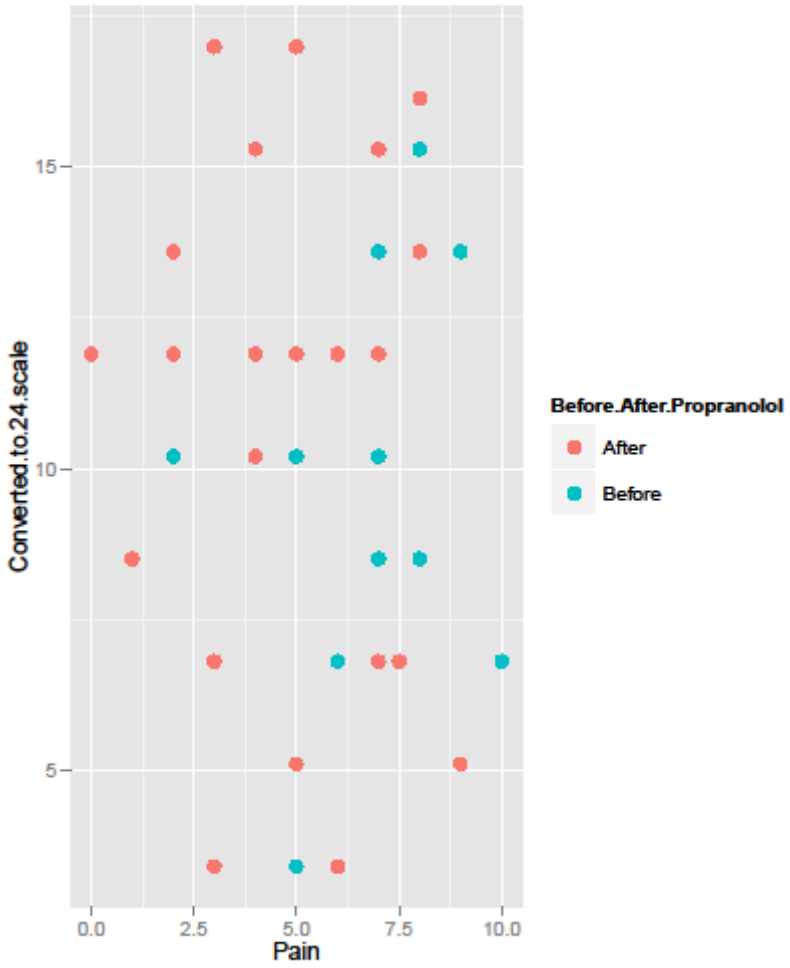


Figure 59. Scatterplot comparing pain before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

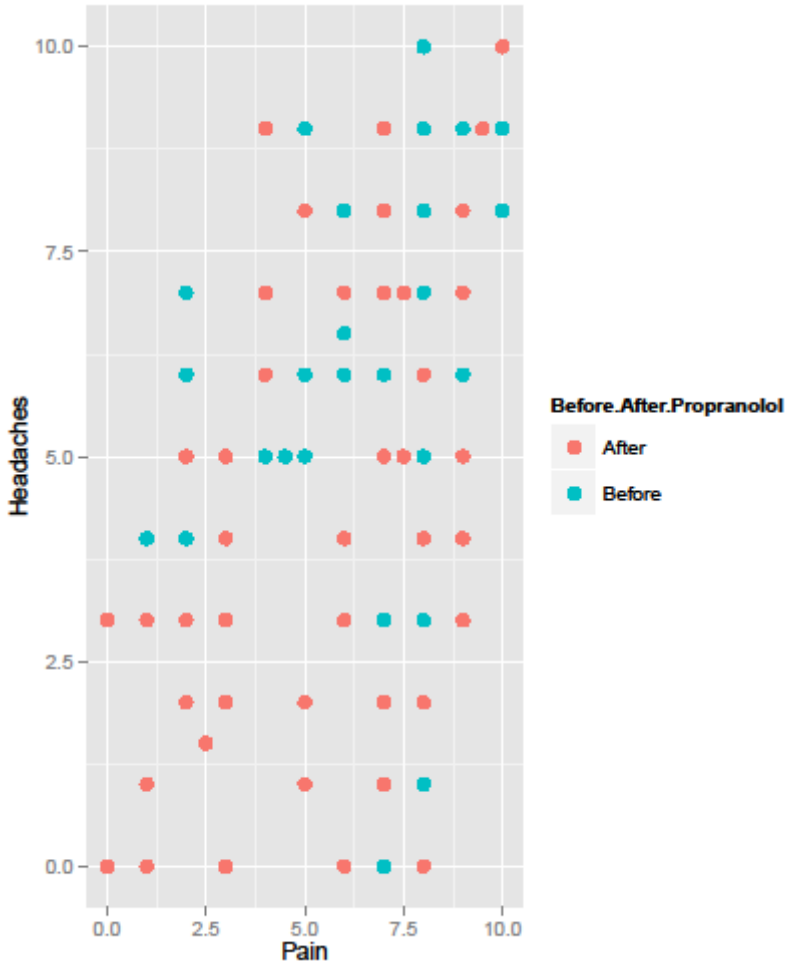


Figure 60. Scatterplot comparing pain before and after propranolol treatment to headaches before and after propranolol treatment.

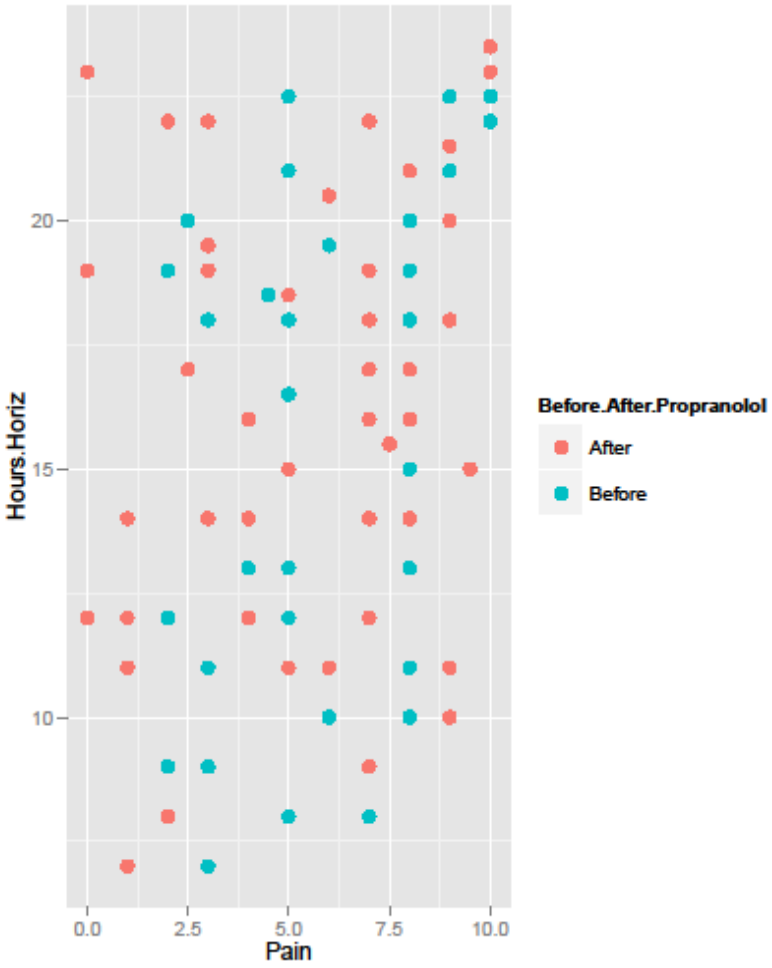


Figure 61. Scatterplot comparing pain before and after propranolol treatment to hours horizontal before and after propranolol treatment.

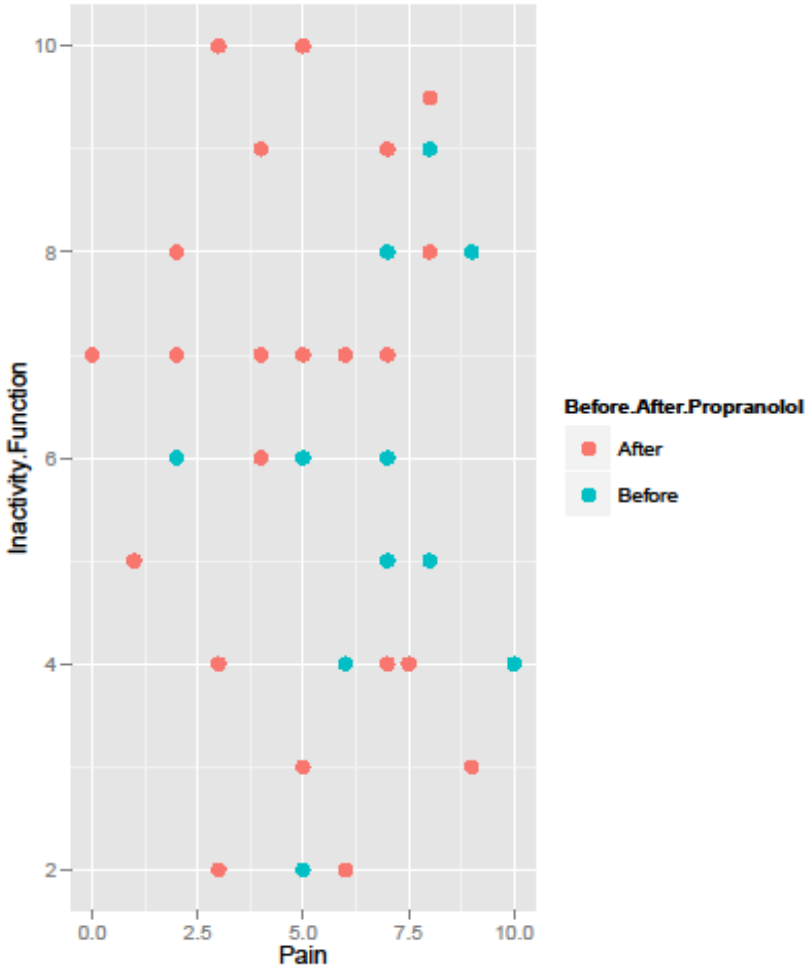


Figure 62. Scatterplot comparing pain before and after propranolol treatment to inactivity/function before and after propranolol treatment.

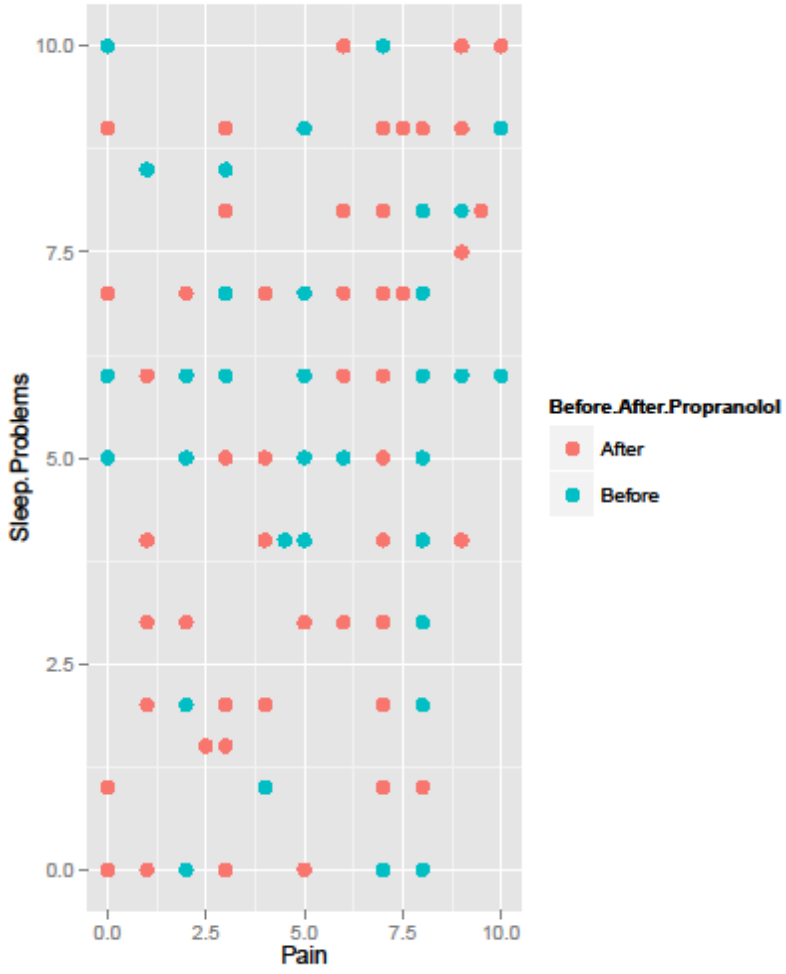


Figure 63. Scatterplot comparing pain before and after propranolol treatment to sleep problems before and after propranolol treatment.

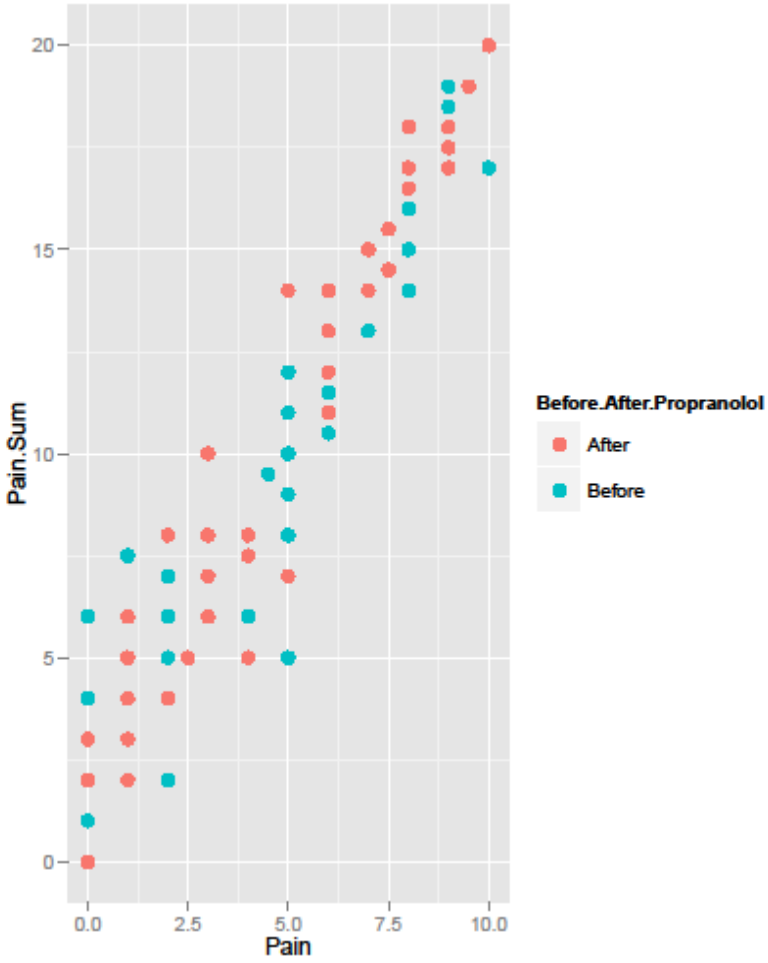


Figure 64. Scatterplot comparing pain before and after propranolol treatment to pain sum before and after propranolol treatment.

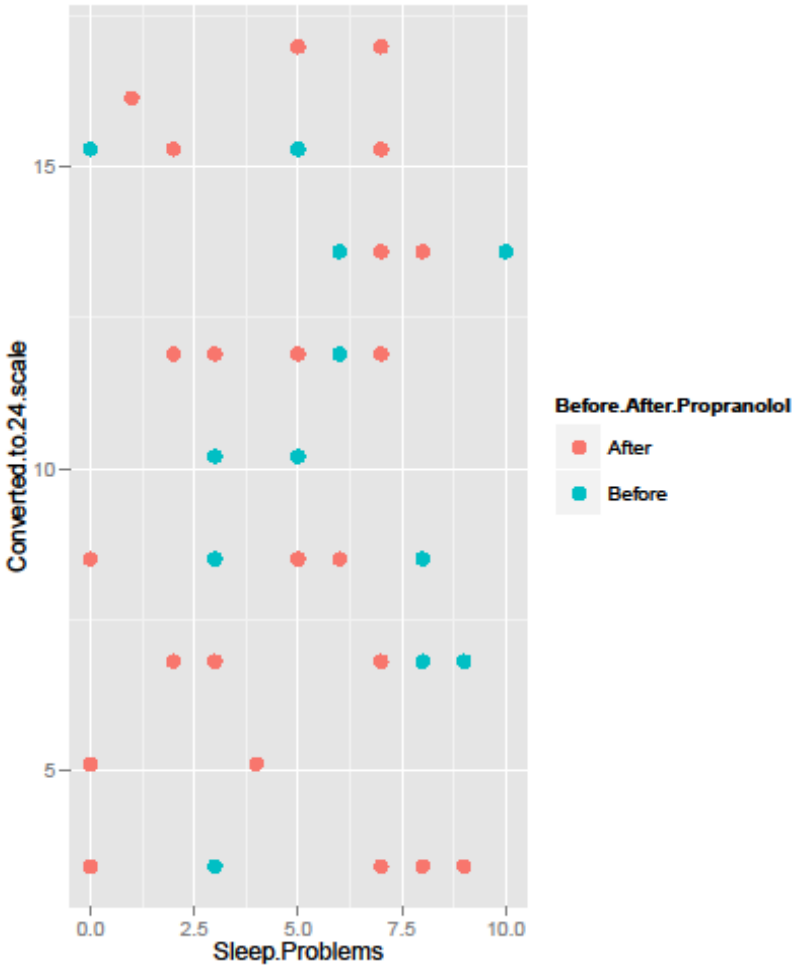


Figure 65. Scatterplot comparing sleep problems before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

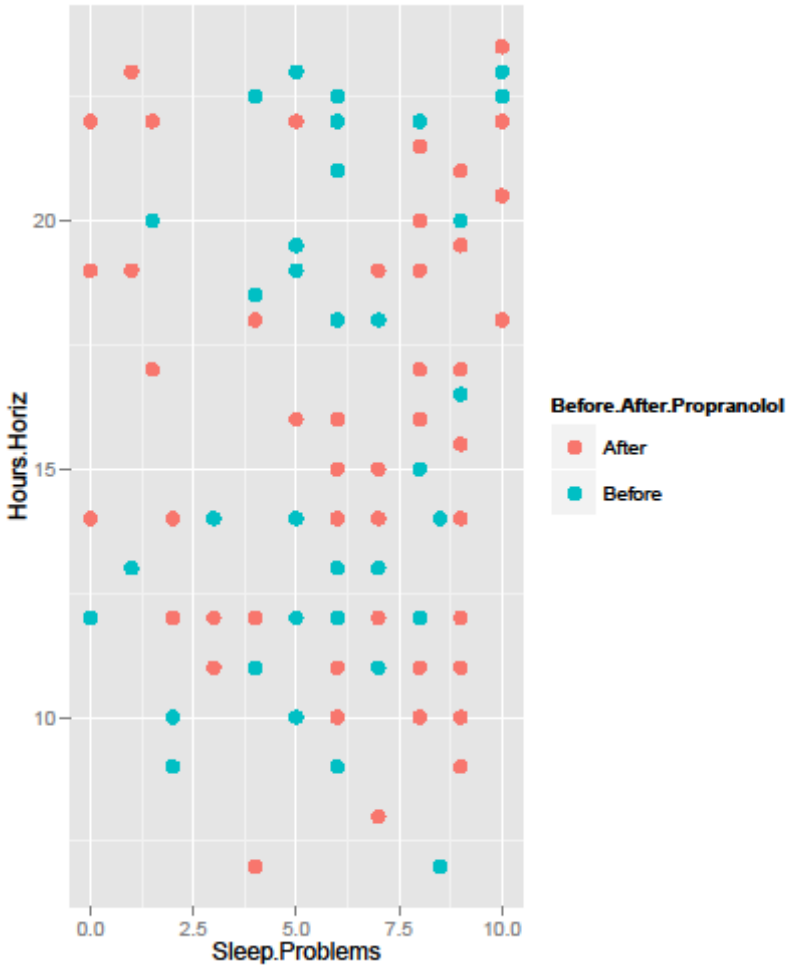


Figure 66. Scatterplot comparing sleep problems before and after propranolol treatment to hours horizontal before and after propranolol treatment.

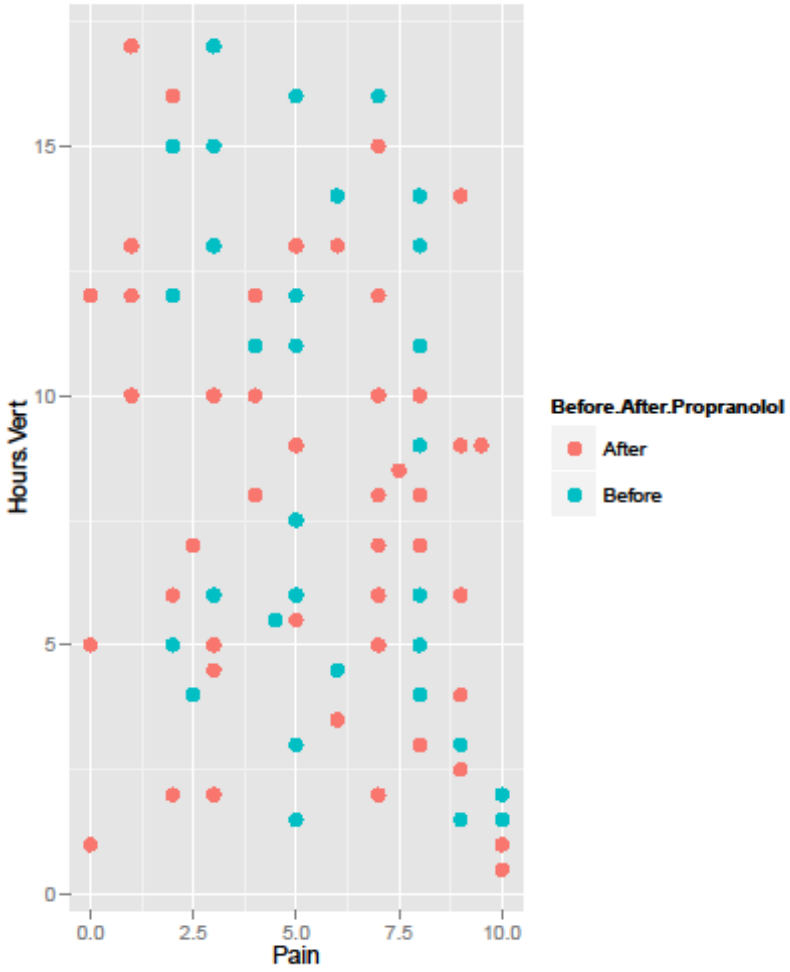


Figure 67. Scatterplot comparing pain before and after propranolol treatment to hours vertical before and after propranolol treatment.

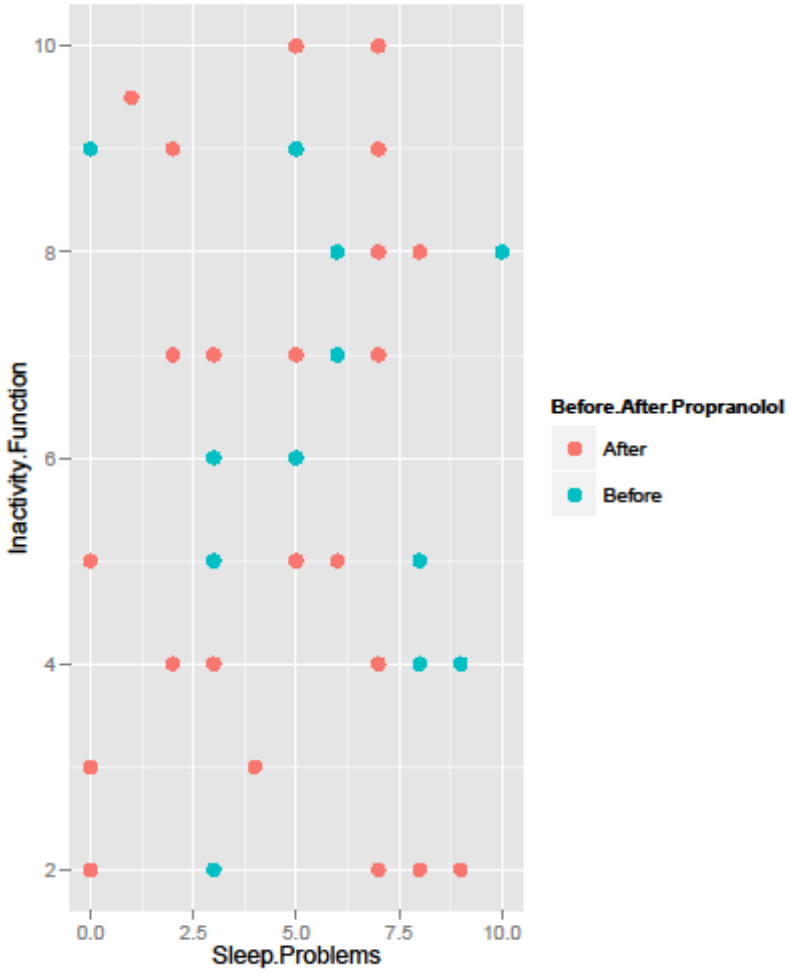


Figure 68. Scatterplot comparing sleep problems before and after propranolol treatment to inactivity/function before and after propranolol treatment.

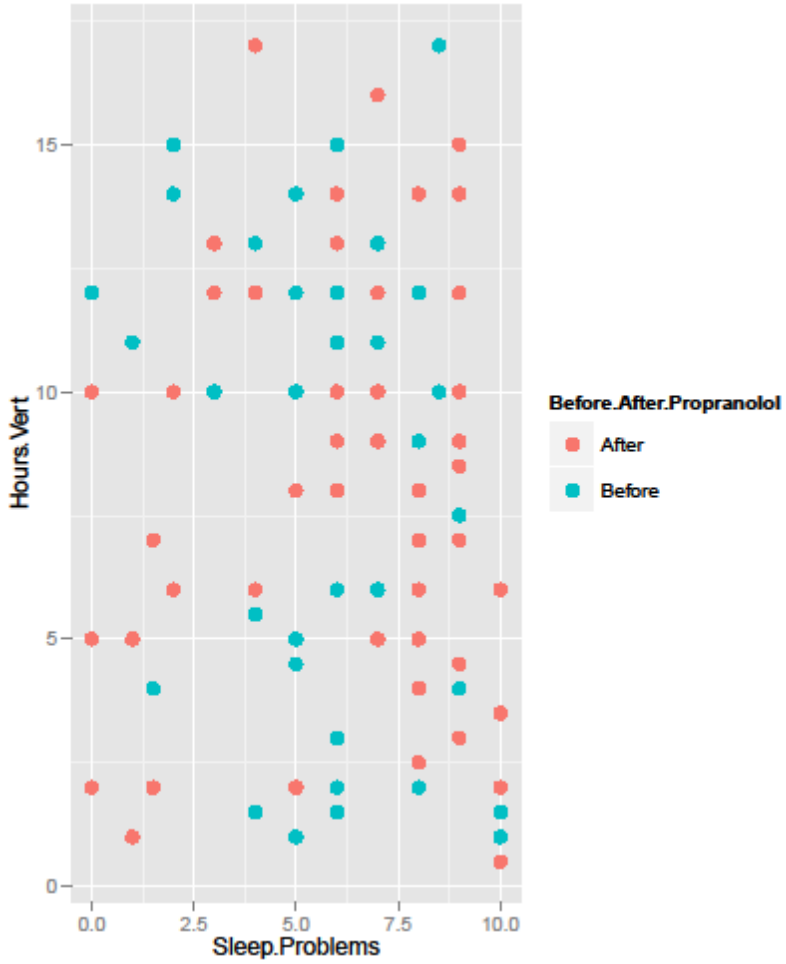


Figure 69. Scatterplot comparing sleep problems before and after propranolol treatment to hours vertical before and after propranolol treatment.

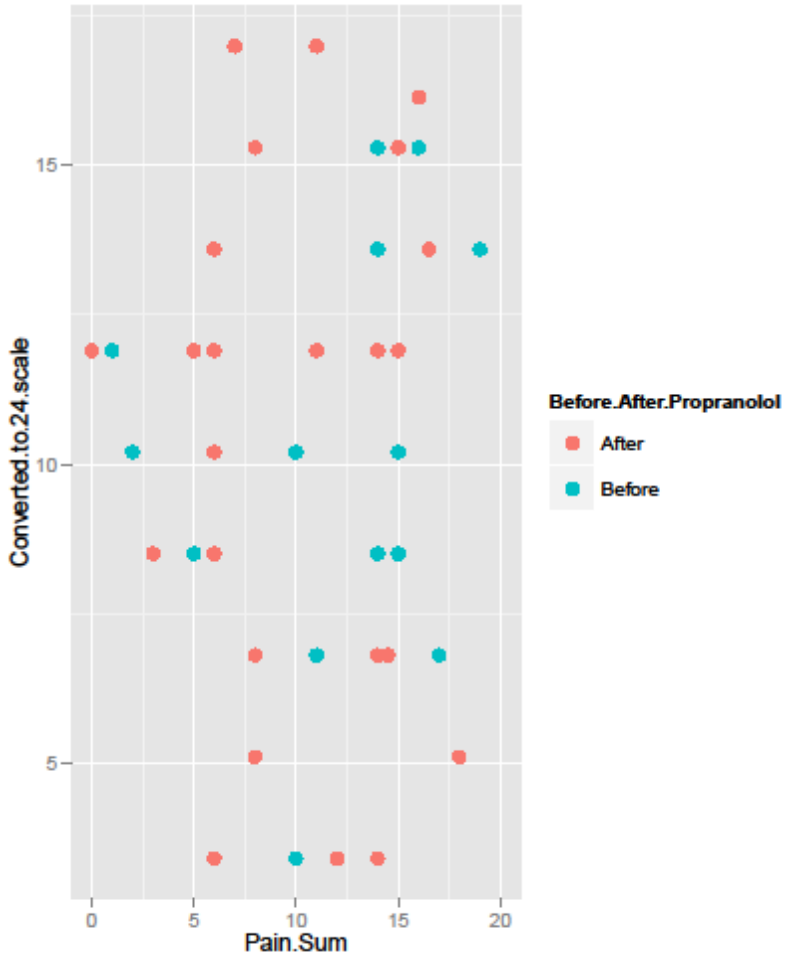


Figure 70. Scatterplot comparing pain sum before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

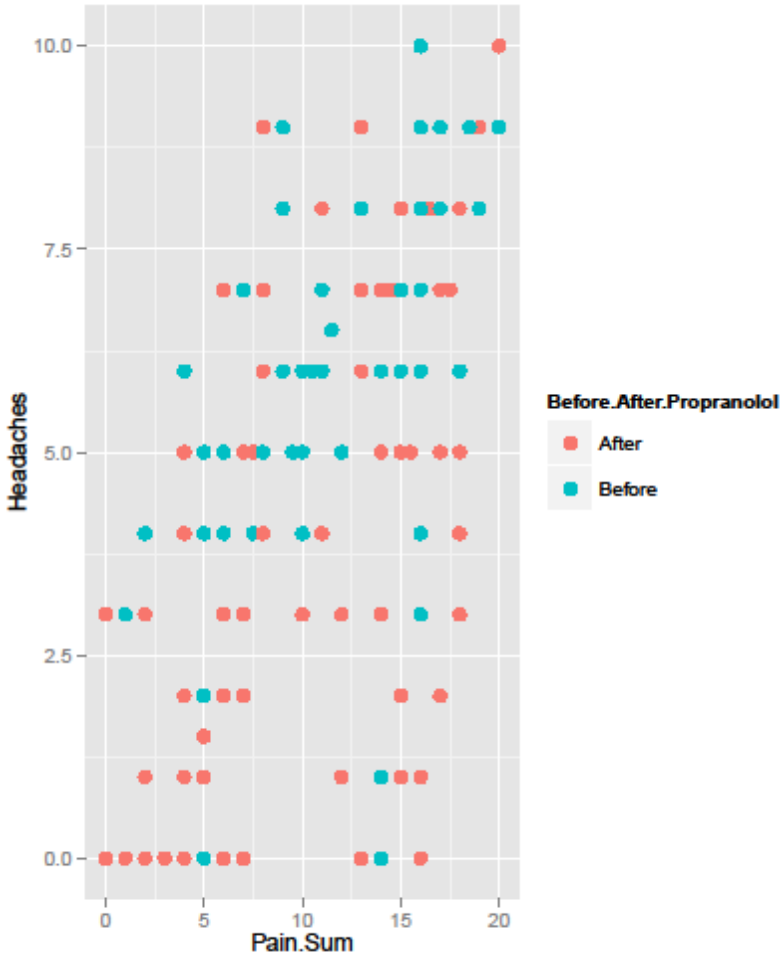


Figure 71. Scatterplot comparing pain sum before and after propranolol treatment to headaches before and after propranolol treatment.

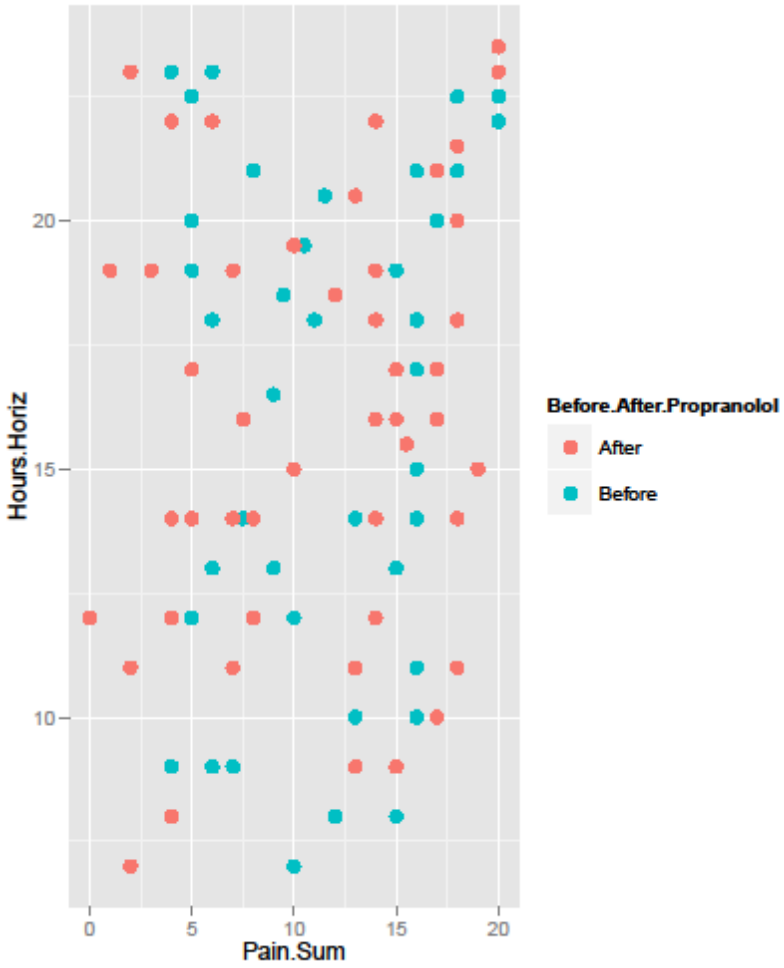


Figure 72. Scatterplot comparing pain sum before and after propranolol treatment to hours horizontal before and after propranolol treatment.

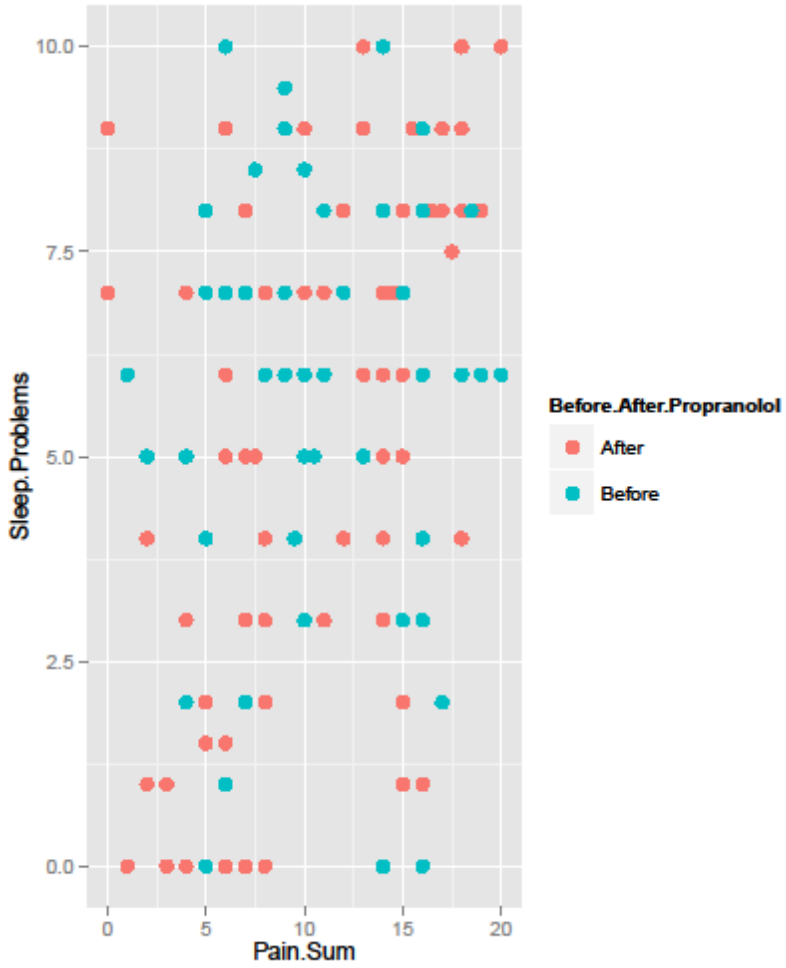


Figure 73. Scatterplot comparing pain sum before and after propranolol treatment to sleep problems before and after propranolol treatment.

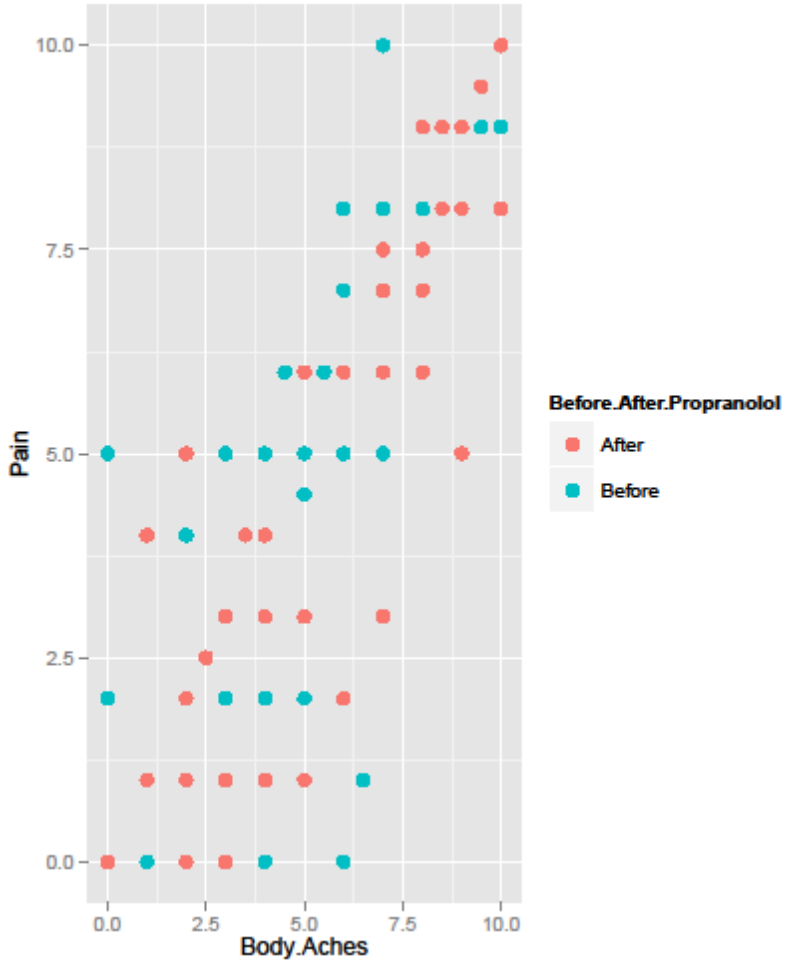


Figure 74. Scatterplot comparing body aches before and after propranolol treatment to pain before and after propranolol treatment.

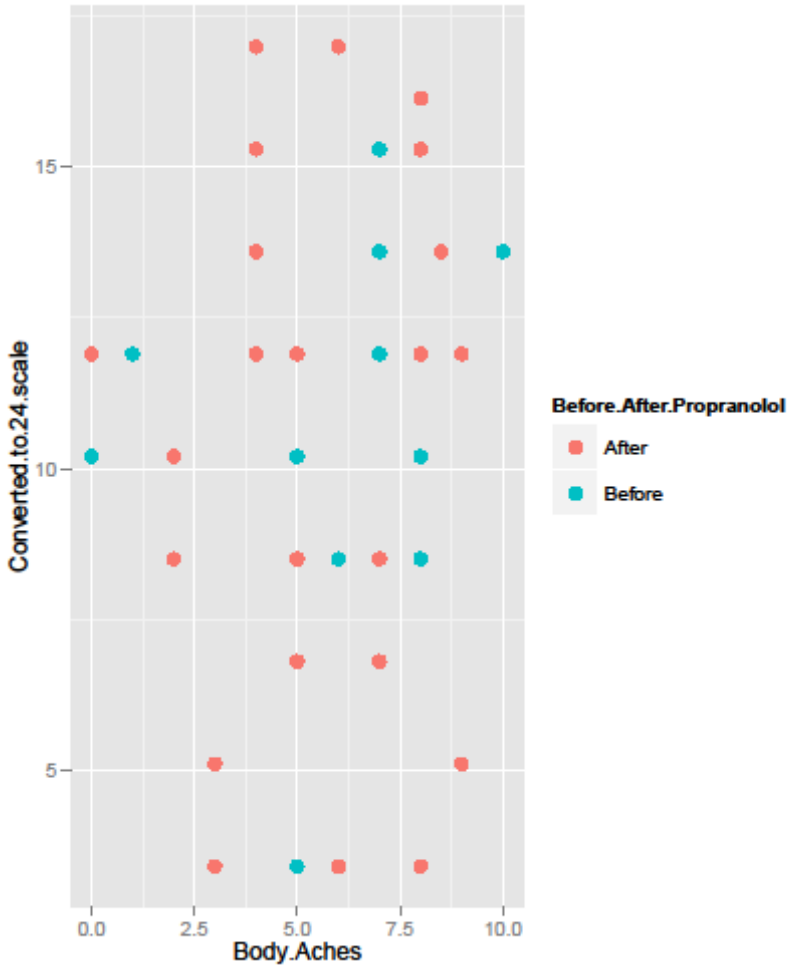


Figure 75. Scatterplot comparing body aches before and after propranolol treatment to activity converted to a 24 hour scale before and after propranolol treatment.

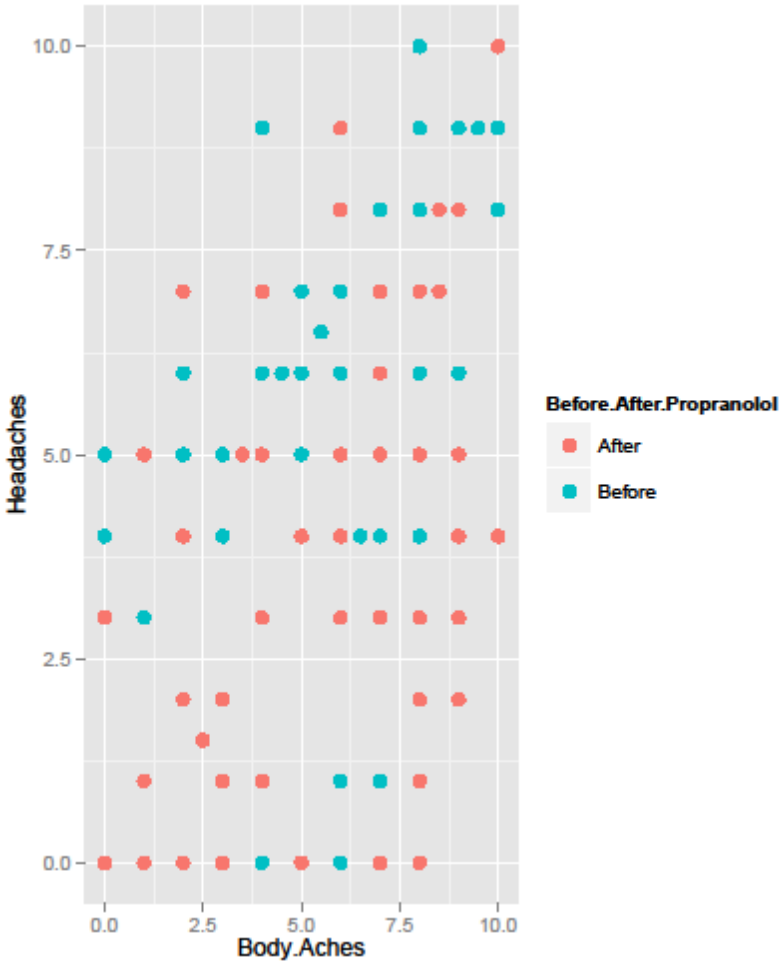


Figure 76. Scatterplot comparing body aches before and after propranolol treatment to headaches before and after propranolol treatment.

APPENDIX E

ANALYSIS BETWEEN VARIABLES

FOR TIME POINTS

Table 3

Parametric and nonparametric statistical tests for significance of each variable.

t-score	degrees of freedom	p-value

Fatigue by Before.After.Propranolol
t = -0.2235, df = 152.502, p-value = 0.8235
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-0.6408787 0.5106266
sample estimates:
mean in group After mean in group Before
7.470588 7.535714
Kruskal-Wallis
chi-squared = 0.0086, df = 1, p-value = 0.9259

Depress.Anxiety by Before.After.Propranolol
t = -0.3757, df = 152.646, p-value = 0.7076
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-1.1143642 0.7582181
sample estimates:
mean in group After mean in group Before
4.779070 4.957143
Kruskal-Wallis
chi-squared = 0.1591, df = 1, p-value = 0.69

Brain.Fog by Before.After.Propranolol
t = -0.5154, df = 151.603, p-value = 0.607
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-0.9057359 0.5309460
sample estimates:
mean in group After mean in group Before
6.341176 6.528571
Kruskal-Wallis
chi-squared = 0.1942, df = 1, p-value = 0.6595

Table 3 Continued

t-score	degrees of freedom	p-value

Body.Aches by Before.After.Propranolol
t = -0.7947, df = 148.496, p-value = 0.428
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-1.189014 0.506941
sample estimates:
mean in group After mean in group Before
5.886905 6.227941
Kruskal-Wallis
chi-squared = 0.3565, df = 1, p-value = 0.5505

Pain by Before.After.Propranolol
t = -1.2264, df = 142.275, p-value = 0.2221
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-1.4983764 0.3510178
sample estimates:
mean in group After mean in group Before
5.349398 5.923077
Kruskal-Wallis
chi-squared = 1.3155, df = 1, p-value = 0.2514

Pain.Sum by Before.After.Propranolol
t = -0.8385, df = 148.95, p-value = 0.4031
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-2.4069919 0.9728182
sample estimates:
mean in group After mean in group Before
11.17262 11.88971
Kruskal-Wallis
chi-squared = 0.5215, df = 1, p-value = 0.4702

Table 3 Continued

t-score	degrees of freedom	p-value

Sleep.Problems by Before.After.Propranolol
t = -1.0838, df = 148.312, p-value = 0.2802
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-1.4264530 0.4159488
sample estimates:
mean in group After mean in group Before
5.553571 6.058824
Kruskal-Wallis
chi-squared = 0.8258, df = 1, p-value = 0.3635

Inactivity.Function by Before.After.Propranolol
t = -0.2772, df = 36.058, p-value = 0.7832
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-1.674050 1.271486
sample estimates:
mean in group After mean in group Before
5.865385 6.066667
Kruskal-Wallis
chi-squared = 0.0365, df = 1, p-value = 0.8485

Converted.to.24.scale by Before.After.Propranolol
t = -0.2772, df = 36.058, p-value = 0.7832
alternative hypothesis: true difference in means is not equal to 0
95 percent confidence interval:
-2.845884 2.161525
sample estimates:
mean in group After mean in group Before
9.971154 10.313333
Kruskal-Wallis
chi-squared = 0.0365, df = 1, p-value = 0.8485

Table 3 Continued

t-score	degrees of freedom	p-value
Hours.Vert by Before.After.Propranolol		
t = -0.1179,	df = 100.135,	p-value = 0.9064
alternative hypothesis: true difference in means is not equal to 0		
95 percent confidence interval:		
-1.868625 1.659024		
sample estimates:		
mean in group After mean in group Before		
8.12069 8.22549		
Kruskal-Wallis		
chi-squared = 0.0037,	df = 1,	p-value = 0.9515
Hours.Horiz by Before.After.Propranolol		
t = -0.1662,	df = 101.179,	p-value = 0.8683
alternative hypothesis: true difference in means is not equal to 0		
95 percent confidence interval:		
-1.928359 1.630185		
sample estimates:		
mean in group After mean in group Before		
15.58621 15.73529		
Kruskal-Wallis		
chi-squared = 0.0311,	df = 1,	p-value = 0.8599

APPENDIX F

REGRESSION MODELING

OF VARIABLES

Table 4

Multiple linear regression model.

Regression model using the response variable of inactivity function converted to a 24 hour scale combined with hours spent vertical

Residuals:

Min	1Q	Median	3Q	Max
-9.1581	-3.9606	0.1539	3.3935	8.7329

Explanatory variables:

Coefficients:

	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	12.37487	1.70976	7.238	3.36e-11 ***
Before.After.PropranololBefore	-0.12265	0.78877	-0.156	0.8767
Fatigue	-0.15188	0.26108	-0.582	0.5617
Depress.Anxiety	-0.22850	0.18348	-1.245	0.2152
Brain.Fog	-0.21206	0.23114	-0.917	0.3606
Body.Aches	0.17733	0.29737	0.596	0.5520
Pain	-0.47863	0.29063	-1.647	0.1020
Headaches	0.30955	0.18589	1.665	0.0982 .
Sleep.Problems	-0.01549	0.17320	-0.089	0.9289

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

Residual standard error: 4.556 on 132 degrees of freedom
(15 observations deleted due to missingness)
Multiple R-squared: 0.1029, Adjusted R-squared: 0.04848
F-statistic: 1.892 on 8 and 132 DF, p-value: 0.06638

APPENDIX G

DEMOGRAPHIC DATA SUMMARY

Table 5

Demographic data summary.

Metric	Count
Females (N)	43
Males (N)	12
Age mean (years)	39
Age range (years)	15 - 76
Mean Propranolol Dose (mg/day)	46
Propranolol Dose Range (mg/day)	12.5 - 180
Mean duration of Propranolol Treatment (Months)	25
Mean Height (cm)	65.8
Mean Weight (lbs)	149.3
Race	
Caucasian	100%
Medications	
NSAIDs	51
Antidepressants	44
Sleep Aids	35
Benzodiazepines	24
Opioids	15
Steroids	6

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